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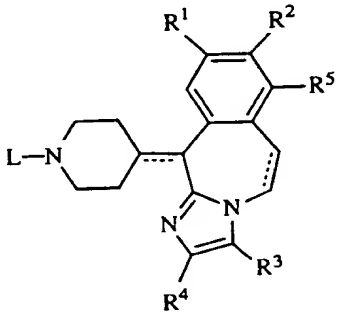
(54) Title: IMIDAZO[2,1-b][3]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE



(I)

(57) Abstract

The present invention is concerned with novel imidazo[2,1-b][3]benzazepines of formula (I), the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein each of the dotted lines independently represents an optional bond; R^1 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy; R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy; R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl; R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo; R^5 represents hydrogen, C_{1-4}alkyl or halo; L represents hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one substituent selected from the group consisting of hydroxy, halo, C_{1-4}alkyloxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkyloxycarbonyl-C_{1-4}alkyloxy, hydroxycarbonylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl, aryloxy and arylcarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl; or, L represents a radical of formula -Alk-Y-Het[1] (a-1), -Alk-NH-CO-Het[2] (a-2) or -Alk-Het[3] (a-3); provided that 6,11-dihydro-11-(4-piperidinylidene)-5*H*-imidazo[2,1-b][3]benzazepine is excluded, which are useful antiallergic compounds. Compositions comprising said compounds, methods of using and processes for preparing the same.

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IMIDAZO[2,1-b][3]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE

Background of the invention

In WO 88/03138 there are described benzo[5,6]cycloheptapyridines which possess antiallergic and anti-inflammatory activity. In EP-A-0,339,978 there are described (benzo- or pyrido)cyclohepta heterocyclics which are useful as PAF antagonists, antihistaminics and/or anti-inflammatory agents.

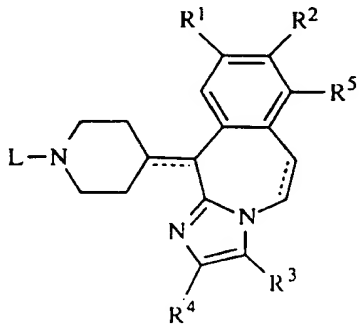
In WO 92/06981 there are described 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine and 1-acetyl-4-(5,6-dihydro-11H-imidazol[1,2-b][3]-benzazepine-11-ylidene)piperidine, the latter of which is useful as a PAF antagonist.

In the J. Med. Chem., 26 (1983), 974-980 there are described some 1-methyl-4-piperidinylidene-9-substituted pyrrolo[2,1-b][3]benzazepine derivatives having neuroleptic properties.

The compounds of the present invention differ structurally from the cited art-known compounds by the fact that the central 7-membered ring invariably contains a nitrogen atom of a fused imidazole ring, and by their favorable antiallergic activity.

Description of the invention

The present invention is concerned with novel imidazo[2,1-b][3]benzazepines of formula



(I),

the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein

each of the dotted lines independently represents an optional bond;

R^1 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen, C_{1-4}alkyl or halo;

L represents hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one substituent selected from the group consisting of hydroxy, halo, C_{1-4}alkyloxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy, hydroxycarbonyl-C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl, aryloxy and arylcarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl;

wherein each aryl is phenyl or phenyl substituted with halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, aminocarbonyl or phenyl substituted with C_{1-4}alkyloxycarbonyl or hydroxycarbonyl; or,

L represents a radical of formula

-Alk-Y-Het^1 (a-1),

-Alk-NH-CO-Het^2 (a-2) or

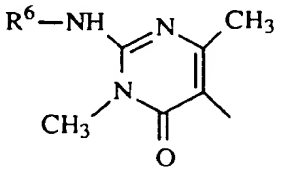
-Alk-Het^3 (a-3); wherein

Alk represents C_{1-4}alkanediyl;

Y represents O, S or NH;

Het^1, Het^2 and Het^3 each represent furanyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4}alkyl substituents; pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxyC_{1-4}alkyl, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl or one or two C_{1-4}alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4}alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4}alkyl, C_{1-4}alkyloxy, amino, hydroxy or halo; imidazo[4,5-c]pyridin-2-yl; and

Het^3 may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C_{1-4}alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



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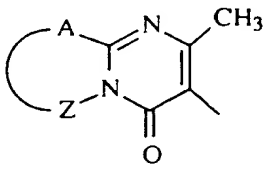
or



(b-2)

wherein

R^6 represents hydrogen or C_{1-4}alkyl; and

A-Z represents -S-CH=CH-, -S-CH_2-CH_2-, -S-CH_2-CH_2-CH_2-, -CH=CH-CH=CH-, -CH_2-CH_2-CH_2-CH_2-, -N(CH_3)-C(CH_3)=CH- or -CH=C(CH_3)-O-;

provided that 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine is ecxluded.

As used in the foregoing definitions halo defines fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl; C_{1-6}alkyl defines C_{1-4}alkyl radicals as defined hereinbefore and the higher homologs thereof having from 5 to 6 carbon atoms such as, for example, pentyl and hexyl; C_{3-6}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 3,3-dimethyl-2-propenyl, hexenyl and the like; C_{1-4}alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 4 carbon atoms such as, for example, methylene, 1,1-ethanediyl, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like.

The term pharmaceutically acceptable addition salt as used hereinbefore defines the non-toxic, therapeutically active addition salt forms which the compounds of formula (I) may form. The compounds of formula (I) having basic properties may be converted into the corresponding therapeutically active, non-toxic acid addition salt forms by treating the free base form with a suitable amount of an appropriate acid following conventional procedures. Examples of appropriate acids are for example, inorganic acids, for example, hydrohalic acid, e.g. hydrochloric, hydrobromic and the like acids, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.
The compounds of formula (I) having acidic properties may be converted in a similar manner into the corresponding therapeutically active, non-toxic base addition salt forms. Examples of such base addition salt forms are, for example, the sodium, potassium, calcium salts, and also the salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, N-methyl-D-glucamine, hydrabamine, amino acids, e.g. arginine, lysine. The term pharmaceutically acceptable addition salts

also comprises the solvates which the compounds of formula (I) may form, e.g. the hydrates, alcoholates and the like.

The term stereochemically isomeric forms as used hereinbefore defines the possible different isomeric as well as conformational forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically and conformationally isomeric forms, said mixtures containing all diastereomers, enantiomers and/or conformers of the basic molecular structure. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some compounds of the present invention may exist in different tautomeric forms and all such tautomeric forms are intended to be included within the scope of the present invention.

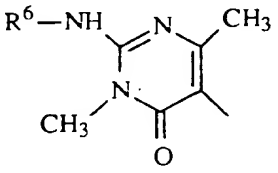
Interesting compounds are those compounds of formula (I) wherein
each of the dotted lines independently represents an optional bond;
R^1 represents hydrogen, halo or C_{1-4}alkyl;
R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;
R^3 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;
R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;
R^5 represents hydrogen;
L represents hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with hydroxy, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl or aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl;
wherein each aryl is phenyl or phenyl substituted with halo, C_{1-4}alkyl or C_{1-4}alkyloxy;
or,
L represents a radical of formula

-Alk-Y-Het^1	(a-1),
-Alk-NH-CO-Het^2	(a-2) or
-Alk-Het^3	(a-3); wherein

Alk represents C_{1-4}alkanediyl;
Y represents O, S or NH;
Het^1, Het^2 and Het^3 each represent furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4}alkyl substituents;

thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4}alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4}alkyl, C_{1-4}alkyloxy, amino, hydroxy or halo; imidazo[4,5-c]pyridin-2-yl; and

Het 3 may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C_{1-4}alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



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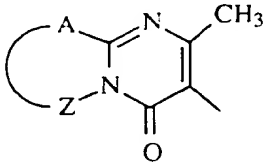


(b-2)

wherein

R^6 represents hydrogen or C_{1-4}alkyl; and

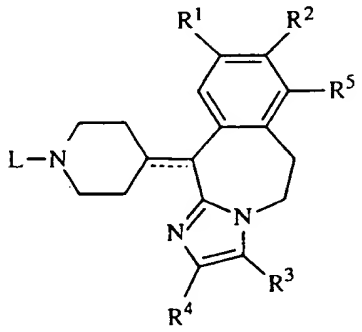
A-Z represents -S-CH=CH-, -S-CH_2-CH_2-, -S-CH_2-CH_2-CH_2-, -CH=CH-CH=CH- or CH_2-CH_2-CH_2-CH_2;

provided that 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine is ecxluded.

Another group of interesting compounds comprises those compounds of formula (I) wherein L is C_{1-4}alkyl or C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl.

Further interesting compounds are those compounds of formula (I) wherein R^1, R^2, R^3, R^4 and R^5 represent hydrogen.

Yet another group of interesting compounds of formula (I) are those of formula



wherein R^1, R^2, R^3, R^4, R^5 and L are as defined under formula (I).

Preferred compounds are those compounds of formula (I) wherein

R^3 represents hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-4}alkyl or hydroxycarbonyl;

R^4 represents hydrogen, halo or hydroxyC_{1-4}alkyl; and

L represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylaminoC_{1-4}alkyl, aryl-C_{1-4}alkyl, propenyl, or

L is a radical of formula (a-1), (a-2) or (a-3), wherein

Het^1, Het^2, and Het^3 each represent furanyl, oxazolyl or thiazolyl each optionally substituted with C_{1-4}alkyl; thiadiazolyl optionally substituted with amino, pyridinyl; or pyrimidinyl each optionally substituted with hydroxy; imidazo[4,5-c]pyridin-2-yl; and Het^3 may also represent a radical of formula (b-2).

More preferred compounds are those preferred compounds wherein

R^1 represents hydrogen or halo;

R^2 represents hydrogen, halo or C_{1-4}alkyloxy; and

L represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, or a radical of formula (a-1), wherein Y represents NH.

Still more preferred are those more preferred compounds wherein

R^4 represents hydrogen or halo; and

L represents hydrogen, C_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl or a radical of formula (a-1), wherein Het^1 is thiazolyl, or imidazo[4,5-c]pyridin-2-yl.

The most preferred compounds are:

5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine;

9-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine;

11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-methanol;

8-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine;

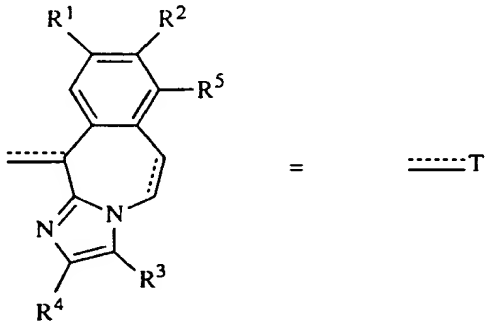
6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-carboxaldehyde;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-carboxylic acid;

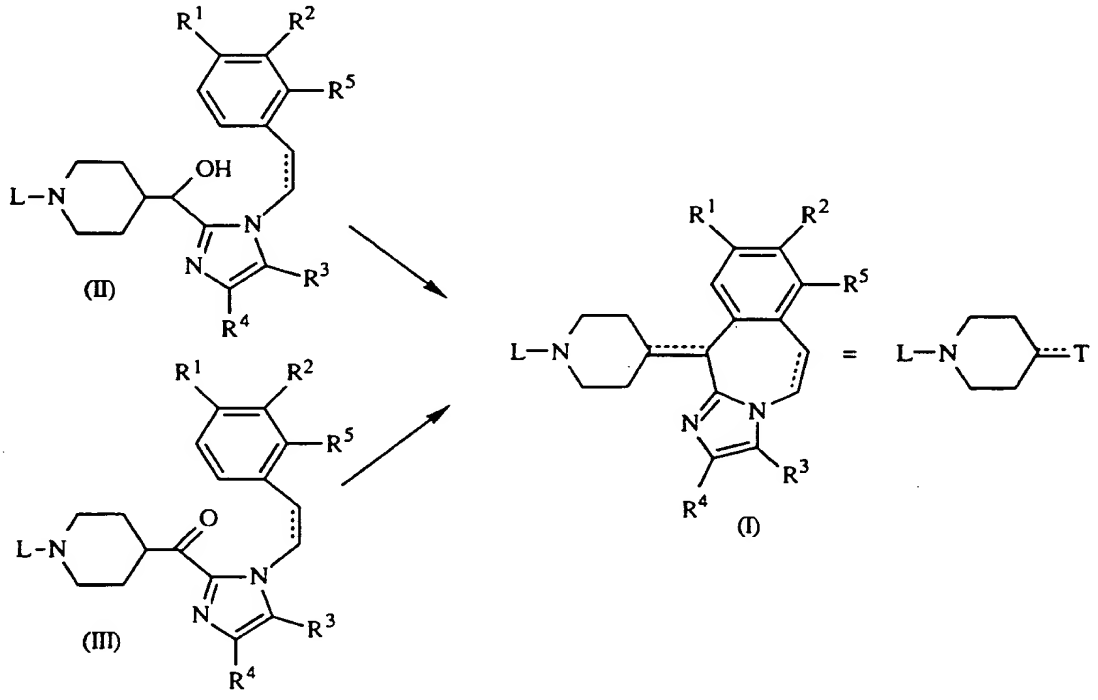
7-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine;

4-(8-fluoro-5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine-propanoic acid dihydrate,
the stereoisomers and the pharmaceutically acceptable acid-addition salts thereof.

In the following paragraphs there are described different ways of preparing the compounds of formula (I). In order to simplify the structural formulae of the compounds of formula (I) and the intermediates intervening in their preparation, the imidazo[2,1-b][3]benzazepine moiety will be represented by the symbol T hereinafter.



The compounds of formula (I) can be prepared by cyclizing an alcohol of formula (II) or a ketone of formula (III).

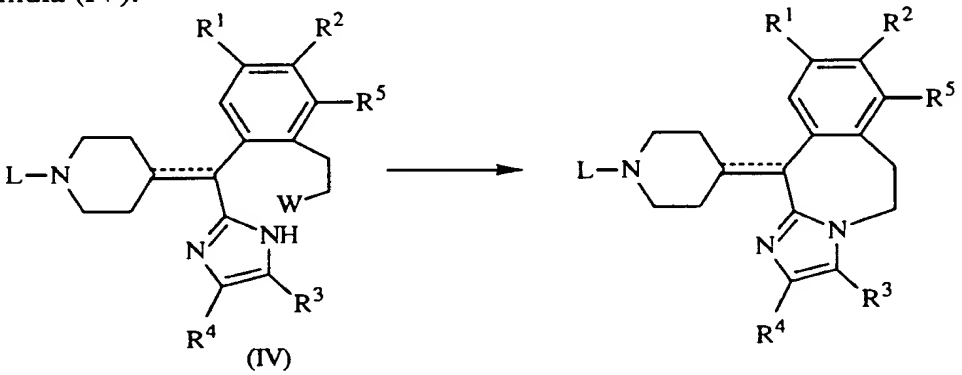


Said cyclization reaction is conveniently conducted by treating the intermediate of formula (II) or (III) with an appropriate acid, thus yielding a reactive intermediate which

cyclizes to a compound of formula (I). Appropriate acids are, for example, strong acids, in particular superacid systems, e.g. methanesulfonic acid, trifluoromethanesulfonic acid, trifluoroacetic acid, methanesulfonic acid / boron trifluoride, hydrofluoric acid / boron trifluoride, or Lewis acids, e.g. aluminum chloride and the like. Obviously, only those compounds of formula (I) wherein L is stable under the given reaction conditions can be prepared according to the above reaction procedure. In case of superacids the reaction is preferably conducted in an excess of said acid; in case of solid Lewis acids, e.g. aluminum chloride, the reaction can be conducted by fusing the starting material and the reagent, preferably in the presence of an additional salt such as sodium chloride. The cyclodehydration reaction with trimethylsilyl iodide is conveniently conducted in a reaction-inert solvent such as, for example, a halogenated hydrocarbon, e.g. trichloromethane. Particularly noteworthy is the fact that the latter reaction also can be performed on intermediates of formula (II) or (III) wherein L represents C_{1-4}alkyloxycarbonyl; in this case - besides cyclodehydration - also cleavage of the carbamate is observed and a compound of formula (I) wherein L is hydrogen is obtained.

In the foregoing and following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

The compounds of formula (I) wherein the central ring of the tricyclic moiety does not contain an optional bond may also be prepared by cyclizing an intermediate of formula (IV).



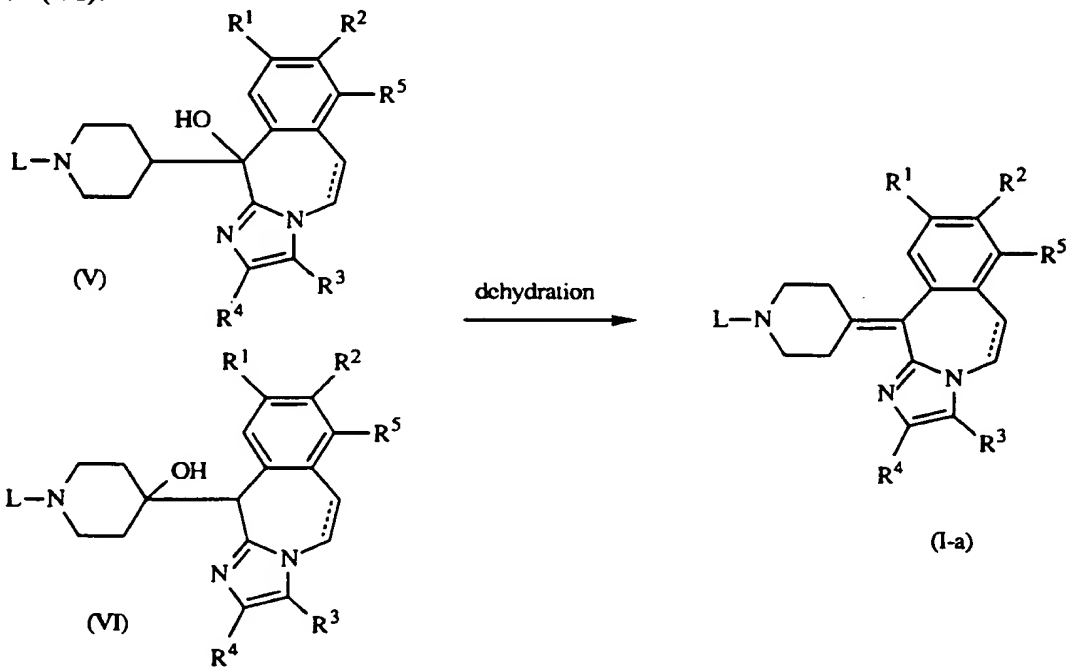
(IV)

In formula (IV) and hereinafter W represents an appropriate leaving group such as, for example, halo, e.g. chloro, bromo and the like; or a sulfonyloxy group such as, for example, methansulfonyloxy, 4-methylbenzenesulfonyloxy and the like.

Said cyclization reaction can conveniently be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; an alkanol, e.g., methanol, ethanol, 1-butanol and the like;

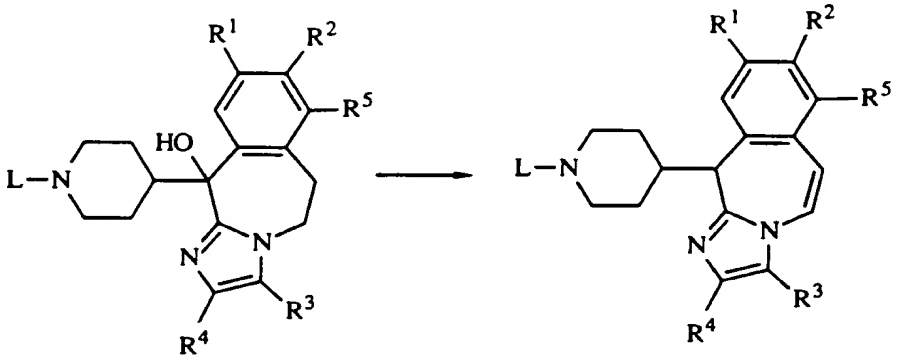
a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., tetrahydrofuran, 1,4-dioxane, 1,1'-oxybisethane and the like; a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone and the like; a halogenated hydrocarbon, e.g. dichloromethane, 1,2-dichloroethane and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium tert. butoxide, sodium hydride, sodium amide, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide and the like; or an organic base, such as, for example, an amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, pyridine and the like may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction.

Alternatively, the compounds of formula (I) wherein a double bond exists between the piperidinyl and the imidazo[2,1-b][3]benzazepine moiety, said compounds being represented by formula (I-a), can be prepared by dehydrating an alcohol of formula (V) or (VI).

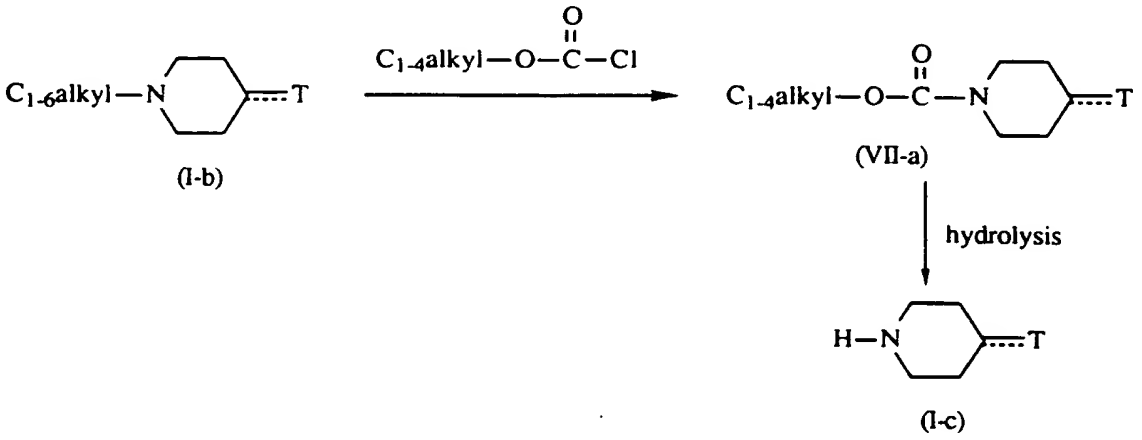


Said dehydration reaction can conveniently be conducted employing conventional dehydrating reagents following art-known methodologies. Appropriate dehydrating

reagents are, for example, acids, e.g. sulfuric acid, phosphoric acid, hydrochloric acid, methanesulfonic acid, carboxylic acids, e.g. acetic acid, trifluoroacetic acid and mixtures thereof; anhydrides, e.g. acetic anhydride, phosphorus pentoxide and the like; other suitable reagents, e.g. zinc chloride, thionyl chloride, boron trifluoride etherate, phosphoryl chloride pyridine, potassium bisulfate, potassium hydroxide. In some instances said dehydration reaction may require heating the reaction mixture, more particularly up to the reflux temperature. Again, only those compounds of formula (I-a) wherein L is stable under the given reaction conditions can be prepared according to the above reaction procedure. Particularly noteworthy is the fact that the latter reaction when performed on intermediate (V) wherein the dotted line does not represent an optional bond, in some instances may also yield a compound of formula (I) with a double bond in the tricyclic moiety and a single bond bridging the tricyclic moiety and the piperidine :



The compounds of formula (I) wherein L is C_{1-6}alkyl, said compounds being represented by the formula (I-b) can be converted into the compounds of formula (I), wherein L is hydrogen, said compounds being represented by the formula (I-c) in a number of manners. A first method involves dealkylating - carbonylating the compounds of formula (I-b) with a C_{1-4}alkylchloroformate and subsequently hydrolyzing the thus obtained compound of formula (VII-a).

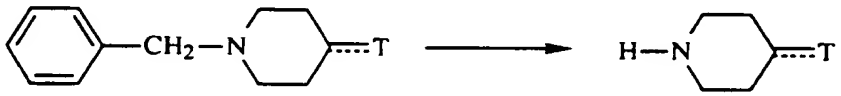


The reaction with the C_{1-4}alkylchloroformate is conveniently conducted by stirring and heating the starting material (I-b) with the reagent in an appropriate solvent and in the presence of a suitable base. Appropriate solvents are, for example, aromatic hydrocarbons, e.g. methylbenzene, dimethylbenzene, chlorobenzene; ethers, e.g. 1,2-dimethoxyethane, and the like solvents. Suitable bases are, for example, alkali or earth alkaline metal carbonates, hydrogen carbonates, hydroxides, or organic bases such as, N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, and the like.

The compounds of formula (VII-a) are hydrolyzed in acidic or basic media following conventional methods. For example, concentrated acids such as hydrobromic, hydrochloric acid or sulfuric acid can be used, or alternatively bases such as alkali metal or earth alkaline metal hydroxides in water, an alkanol or a mixture of water-alkanol may be used. Suitable alkanols are methanol, ethanol, 2-propanol and the like. In order to enhance the rate of the reaction it is advantageous to heat the reaction mixture, in particular up to the reflux temperature.

The compounds of formula (I-b) may also be converted directly into the compounds of formula (I-c) by stirring and heating them with an α-halo-C_{1-4}alkyl chloroformate in an appropriate solvent such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane; an aromatic hydrocarbon, e.g. methylbenzene, dimethylbenzene; an ether, e.g. 1,2-dimethoxyethane; an alcohol, e.g. methanol, ethanol, 2-propanol, optionally in the presence of a base such as, for example, an alkali or earth alkaline metal carbonate, hydrogen carbonate, hydroxide or an amine, e.g. N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, and the like.

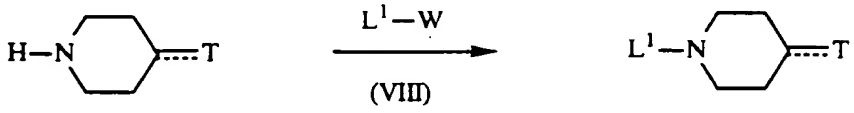
The compounds of formula (I-c) can also be prepared by debenzylating a compound of formula (I-d) by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent.



(I-d) (I-c)

A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said debenzylation reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

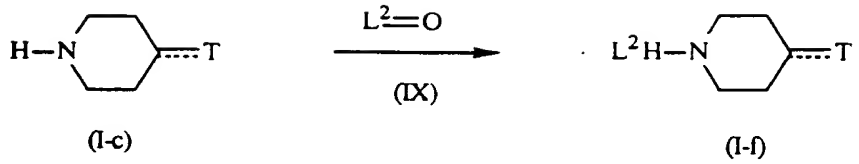
The compounds of formula (I) wherein L is other than hydrogen, said compounds being represented by formula (I-e) and said L by L^1, can be prepared by N-alkylating the compounds of formula (I-c) with a reagent of formula L^1-W (VIII).



(I-c) (I-e)

Said N-alkylation reaction can conveniently be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; an alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., tetrahydrofuran, 1,4-dioxane, 1,1'-oxybisethane and the like; a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone and the like; a halogenated hydrocarbon, e.g. dichloromethane, 1,2-dichloroethane and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium tert. butoxide, sodium hydride, sodium amide, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide and the like; or an organic base, such as, for example, an amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, pyridine and the like may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction. Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions.

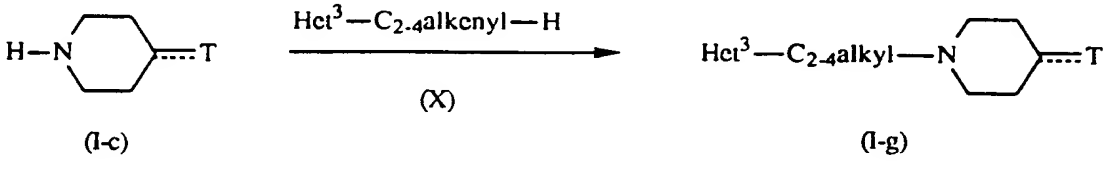
The compounds of formula (I) wherein L is C_{1-6}alkyl or substituted C_{1-6}alkyl, said L being represented by the radical L^2H- and said compounds by formula (I-f), can also be prepared by reductive N-alkylation of the compounds of formula (I-c) with an appropriate ketone or aldehyde of formula L^2=O (IX). L^2=O represents an intermediate of formula L^2H_2 wherein two geminal hydrogen atoms have been replaced by oxygen (=O) and L^2 is a geminal bivalent C_{1-6}alkylidene radical which optionally may be substituted.



(I-c) (IX) (I-f)

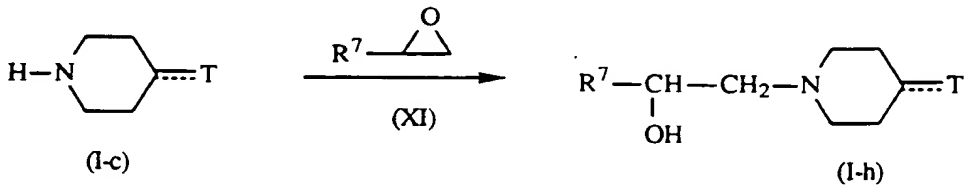
Said reductive N-alkylation reaction may conveniently be carried out by reducing a mixture of the reactants in a suitable reaction-inert solvent following art-known reductive N-alkylation procedures. In particular, the reaction mixture may be stirred and/or heated in order to enhance the reaction rate. Suitable solvents are, for example, water; C_{1-6}alkanols, e.g. methanol, ethanol, 2-propanol and the like; esters, e.g. ethyl acetate, γ-butyrolactone and the like; ethers, e.g. 1,4-dioxane, tetrahydrofuran, 1,1'-oxybis-ethane, 2-methoxyethanol and the like; halogenated hydrocarbons, e.g. dichloro-methane, trichloromethane and the like; dipolar aprotic solvents, e.g. N,N-dimethyl-formamide, dimethyl sulfoxide and the like; carboxylic acids, e.g. acetic acid, propanoic acid and the like; or a mixture of such solvents. The term "art-known reductive N-alkylation procedures" means that the reaction is carried out either with sodium cyanoborohydride, sodium borohydride, formic acid or a salt thereof, e.g. ammonium formate and the like reducing agents, or alternatively under hydrogen atmosphere, optionally at an increased temperature and/or pressure, in the presence of an appropriate catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene, quinoline-sulphur and the like. In some instances it may also be advantageous to add an alkali metal salt to the reaction mixture such as, for example, potassium fluoride, potassium acetate and the like salts.

The compounds of formula (I) wherein L represents a radical Het^3-C_{2-4}alkyl, said compounds being represented by formula (I-g) can be prepared by the addition reaction of a compound of formula (I-c) to an appropriate alkene of formula (X).



(I-c) (X) (I-g)

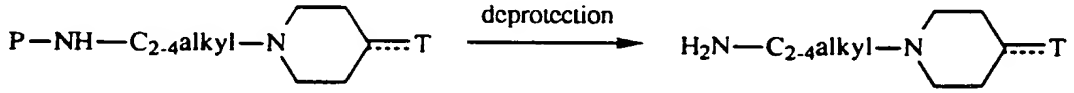
The compounds wherein L is 2-hydroxy-C_{2-6}alkyl, or aryloxy-2-hydroxy-C_{2-6}alkyl said compounds being represented by formula (I-h), can be prepared by reacting a compound of formula (I-c) with an epoxide (XI) wherein R^7 represents hydrogen, C_{1-4}alkyl or aryloxyC_{1-4}alkyl.



(I-c) (I-h)

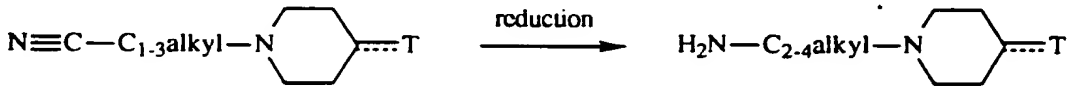
The reaction of (I-c) with respectively (X) or (XI) can be conducted by stirring and, if desired, heating the reactants in a reaction-inert solvent such as, for example, a ketone, e.g. 2-propanone, 4-methyl-2-pentanone; an ether, e.g. tetrahydrofuran; an alcohol, e.g. methanol, ethanol, 1-butanol; a dipolar aprotic solvent, e.g. N,N-dimethylformamide and the like.

The compounds of formula (VII-b) can be prepared from a compound of formula (I-i) wherein L represents P-NH-C_{2-4}alkyl and P is a protective group such as, for example, C_{1-4}alkyloxycarbonyl, following art-known deprotection methods.



(I-i) (VII-b)

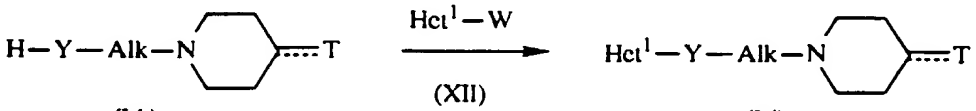
The compounds of formula (VII-b) can also be prepared by reducing a compound of formula (VII-c).



(VII-c) (VII-b)

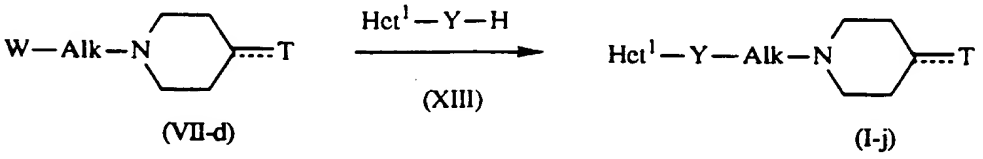
Said reduction can be conducted by stirring and, if desired, heating the starting material in a hydrogen containing medium in the presence of a catalyst, e.g. palladium-on-charcoal, platinum-on-charcoal, Raney Nickel and the like, in a suitable solvent, e.g. methanol, ethanol and the like, or by reduction with a metal hydride, e.g. lithium aluminum hydride in an ether, e.g. tetrahydrofuran.

The compounds of formula (I) wherein L is a radical of formula -Alk-Y-Het^1, said compounds being represented by formula (I-j), can be prepared by alkylating a compound of formula (I-k) with a reagent of formula (XII).



(I-k) (I-j)

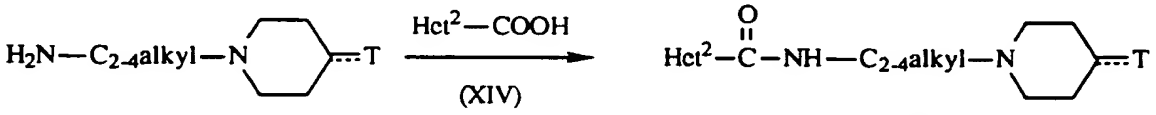
Alternatively, the compounds of formula (I-j) can also be prepared by reacting a compound of formula (VII-d) with a reagent of formula (XIII).



(VII-d) (I-j)

The above alkylation reactions may conveniently be conducted in a reaction-inert solvent, e.g. methylbenzene, dimethylbenzene, 2-propanone, 4-methyl-2-pentanone, 1,4-dioxane, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, methanol, ethanol, 1-butanol and the like. The addition of an appropriate base, e.g. an alkali metal or earth alkaline metal carbonate or hydrogen carbonate, sodium hydride, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be used to pick up the acid liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. In order to enhance the rate of the reaction the reaction mixture may be heated.

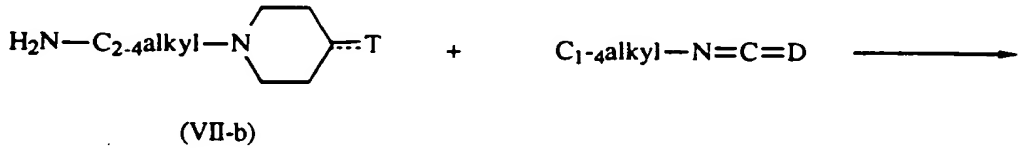
The compounds of formula (I) wherein L represents a radical of formula -Alk-NH-CO-Het^2, said compounds being represented by formula (I-l) can be prepared by N-acylating a compound of formula (VII-b) with a carboxylic acid of formula (XIV) or a reactive functional derivative thereof.



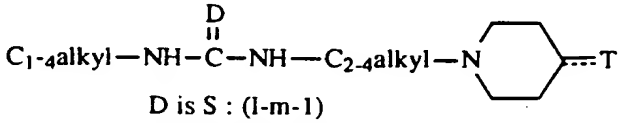
(VII-b) (I-l)

The reaction of (XIV) with (VII-b) may generally be conducted following art-known amidation reaction procedures. For example, the carboxylic acid may be converted into a reactive derivative, e.g. an anhydride or a carboxylic acid halide, which subsequently is reacted with (VII-b); or by reacting (XIV) and (VII-b) with a suitable reagent capable of forming amides, e.g., N,N-methanetetraylbis[cyclohexamine], 2-chloro-1-methyl-pyridinium iodide and the like. Said reactions are conveniently conducted in a suitable solvent such as, for example, an ether, e.g., tetrahydrofuran, a halogenated hydrocarbon, e.g., dichloromethane, trichloromethane, a dipolar aprotic solvent and the like. The addition of a base such as, for example, N,N-diethylethanamine and the like may be appropriate.

The compounds of formula (I) wherein L represents C_{1-4}alkylamino(thio)carbonyl-aminoC$_{1-4}$alkyl, said compounds being represented by the formula (I-m), can be prepared from the compounds of formula (VII-b) by reaction with a C_{1-4}alkyliso(thio)-cyanate in a reaction-inert solvent such as, for example, an ether, e.g. tetrahydrofuran.

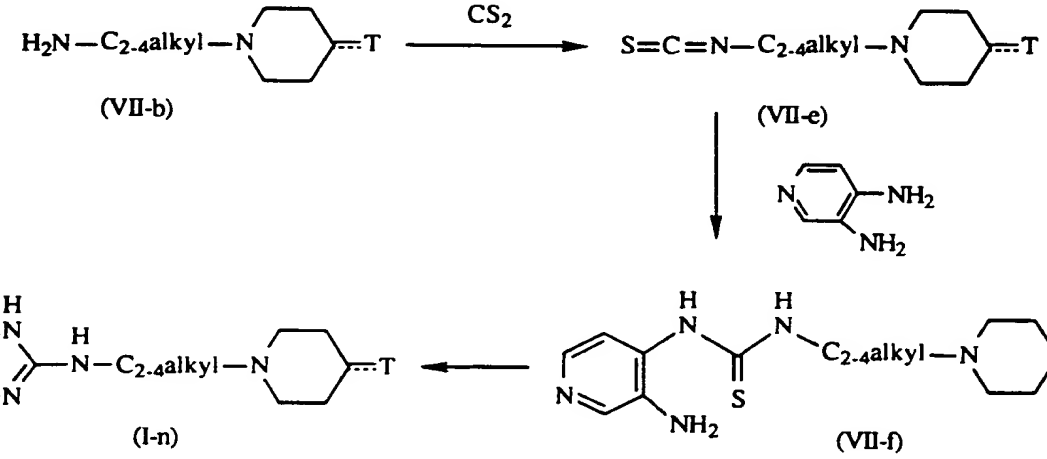


(VII-b)



D is S : (I-m-1)
D is O : (I-m-2)

The compounds of formula (I) wherein Het^1 represents an imidazo[4,5-c]pyridin-2-yl radical and Y represents NH, said compounds being represented by formula (I-n) can be prepared from a compound of formula (VII-b) according to the following reaction scheme.

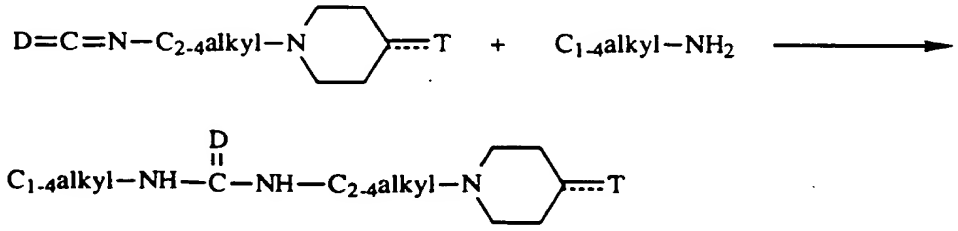


(VII-b) (VII-e) (I-n) (VII-f)

The isocyanate (VII-e) is prepared by reacting (VII-b) with carbon disulfide in the presence of a dehydrating reagent such as N,N-methanetetraylbis[cyclohexanamine] in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran. The isothiocyanate is reacted with 3,4-diaminopyridine in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran, and the resulting thiourea is cyclized by treatment with an appropriate metal oxide such as mercury(II)oxide. In certain instances if may be appropriate to supplement the reaction mixture with a small amount of sulfur.

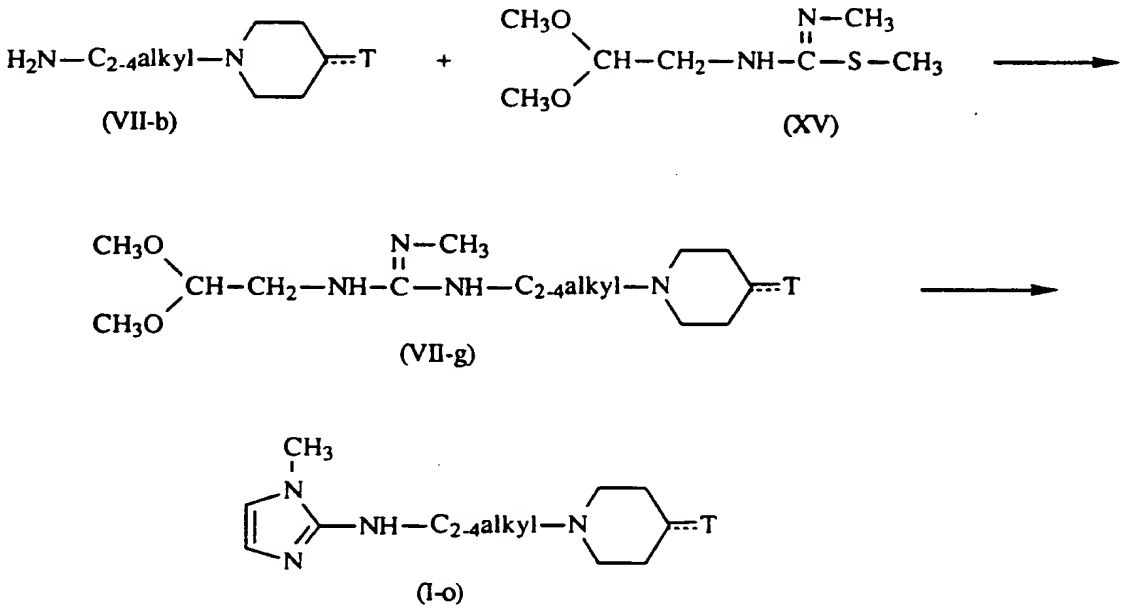
The compound (VII-e) or the corresponding isocyanate can also be employed to prepare compounds of formula (I-m), by reacting (VII-e) or the corresponding

isocyanate with a C_{1-4}alkylamine in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran.



D is S : (I-m-1)
D is O : (I-m-2)

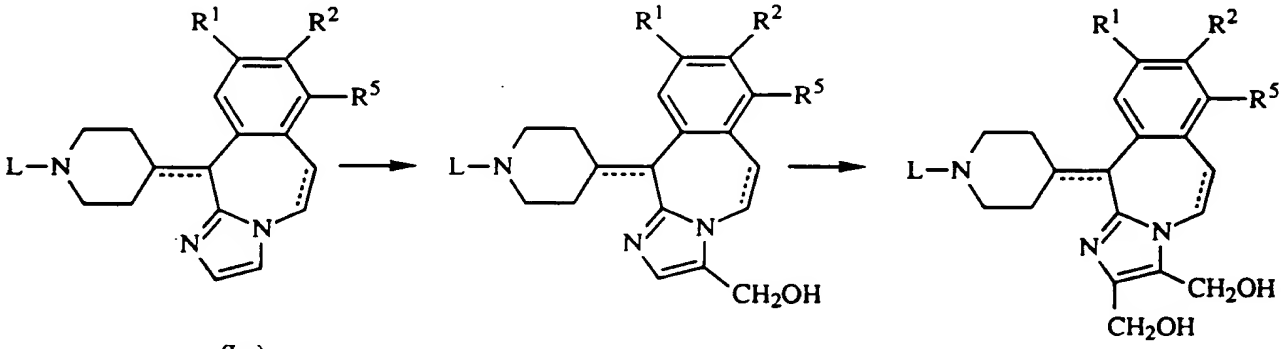
The compounds of formula (I) wherein Het^1 represents an imidazole and Y represents NH, said compounds being represented by formula (I-o) can be prepared from the compounds (VII-b) according to the following reaction scheme.



The compound (VII-b) is reacted with a reagent of formula (XV) in a reaction-inert solvent such as an alcohol, e.g. 2-propanol and the thus obtained intermediate (VII-g) is cyclized by treatment with an acidic aqueous solution, such as a hydrochloric acid aqueous solution.

The compounds of formula (I) wherein R^3 and/or R^4 represent hydroxymethyl can be prepared by formylating the compounds of formula (I), wherein R^3 and/or R^4 are hydrogen, said compounds being represented by the formula (I-p) with formaldehyde, optionally in the presence of an appropriate carboxylic acid - carboxylate mixture such

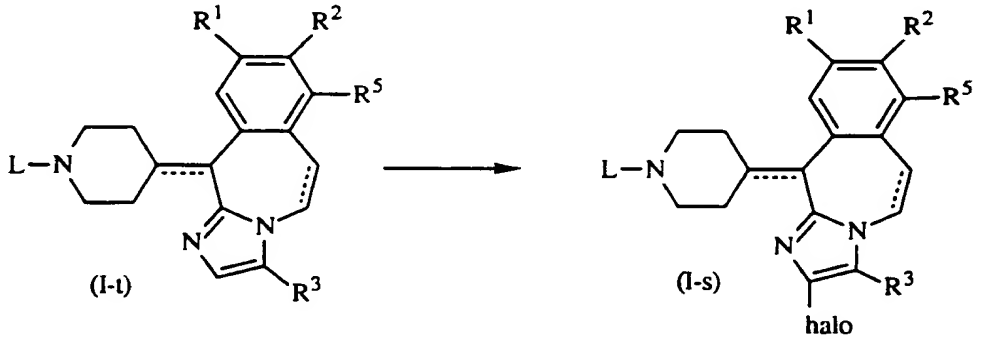
as, for example, acetic acid - sodium acetate and the like. In order to enhance the rate of the reaction, the reaction mixture is advantageously heated up to the reflux temperature.



(I-p) (I-q) (I-r)

The thus obtained compounds (I-q) and (I-r) can be further oxidized to the corresponding aldehyde or carboxylic acid by reaction with suitable reagents such as, for example, manganese(IV)oxide, respectively, silver nitrate.

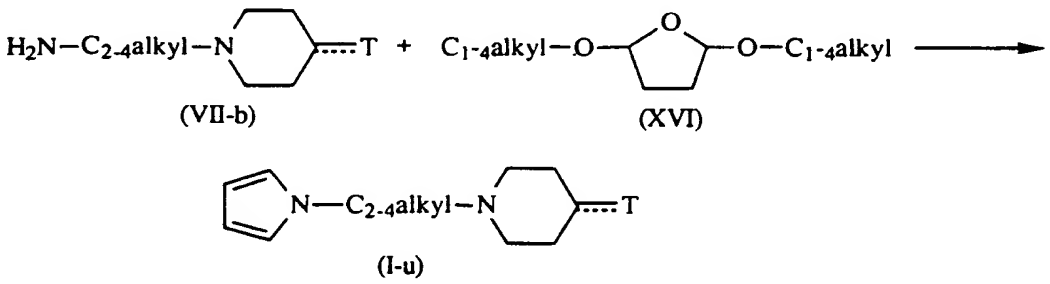
The compounds of formula (I) wherein R^4 is halo, said compounds being represented by formula (I-s), can be prepared by halogenating the compounds of formula (I), wherein R^4 is hydrogen, said compounds being represented by the formula (I-t).



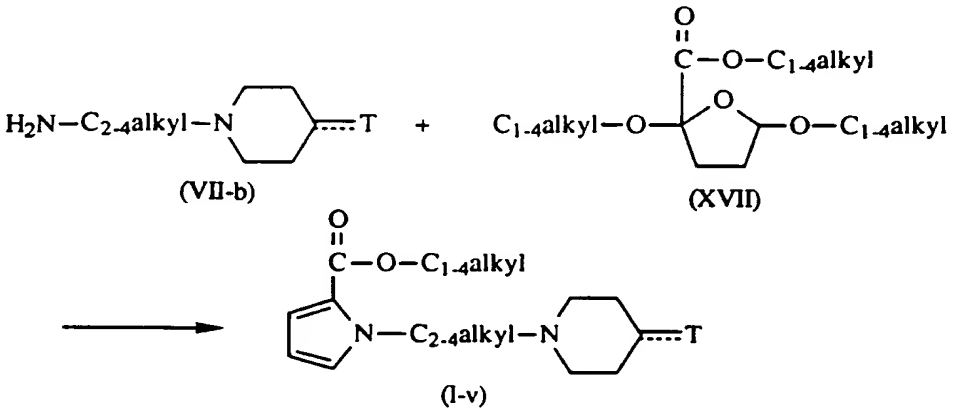
(I-t) (I-s)

Said halogenation reaction can conveniently be conducted by treating the starting material with dihalide in an appropriate solvent such as, for example, a carboxylic acid, e.g. acetic acid, optionally in admixture with a carboxylate salt, e.g. sodium acetate. In order to enhance the rate of the reaction, the reaction mixture may be heated.

The compounds of formula (I) wherein Het^3 represents a pyrrolyl radical, said compounds being represented by the formula (I-u), can be prepared by reacting a compound of formula (VII-b) with a reagent of formula (XVI).

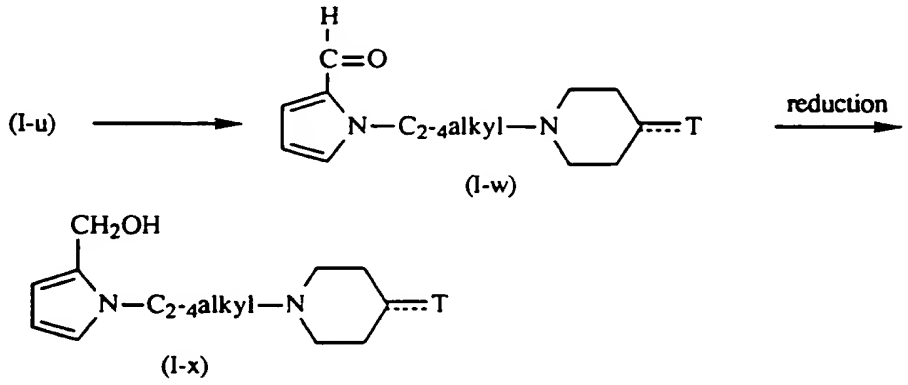


In a similar way, the compounds of formula (I) wherein Het^3 represents a 2-C_{1-4}alkyloxycarbonyl-1-pyrrolyl radical, said compounds being represented by the formula (I-v), can be prepared by reacting a compound of formula (VII-b) with a reagent of formula (XVII).



The above reactions of (VII-b) with (XVI) and (XVII), respectively, preferably are conducted in the presence of an acid, such as, for example, acetic acid.

Further, the compounds of formula (I-u) may be converted in the corresponding aldehyde and alcohol compounds, said compounds being represented by the formulae (I-w) and (I-x), respectively, by the following reaction sequence.

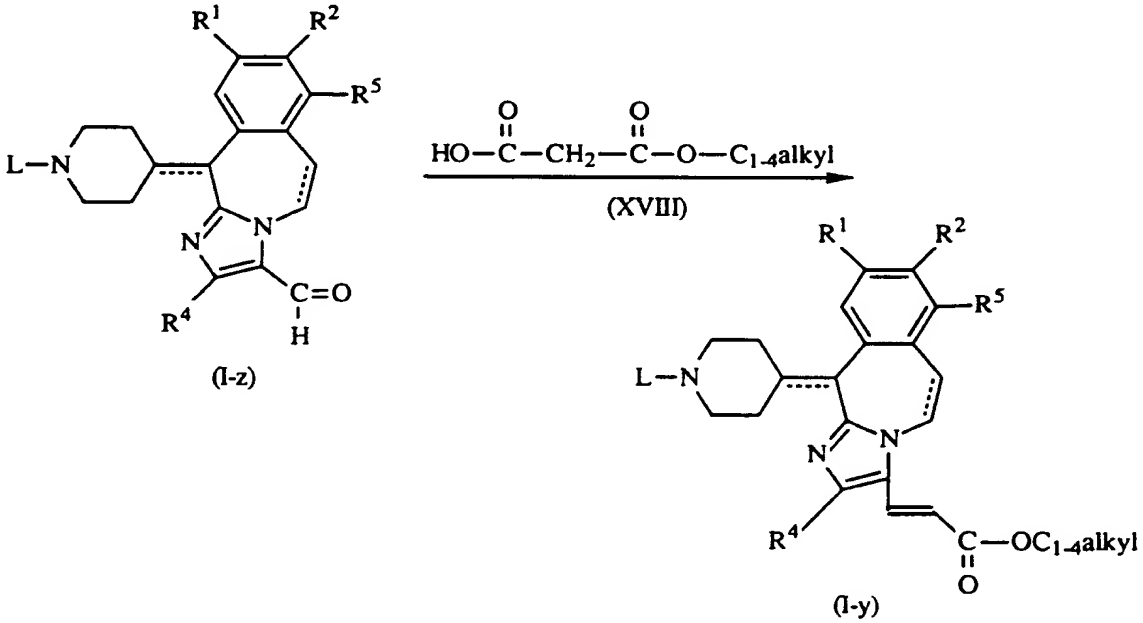


The formylation of (I-u) into (I-w) can conviently be conducted in a reaction-inert solvent such as, for example, a dipolar aprotic solvent, e.g. N,N-dimethylformamide,

N,N-dimethylacetamide and the like, in the presence of a formylating reagent such as, for example, phosphoryl chloride, zinc cyanide and hydrochloric acid, trichloromethane and hydroxide ions, and the like. The compounds of formula (I-w) can be reduced into the compounds of formula (I-x) in a reaction-inert solvent, such as, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like in the presence of an appropriate reductant, such as, for example, metallic hydrides, e.g. lithium aluminium hydride, sodium borohydride, sodium cyanoborohydride, and the like.

The compounds of formula (I-v) and (I-w), can be converted in the corresponding compounds of formula (I) wherein Het^3 is a 2-hydroxycarbonyl-1-pyrrolyl radical by the hydrolysis of (I-v) in the presence of an acid or a base, or oxidation of (I-w) in the presence of a suitable oxidizing reagent.

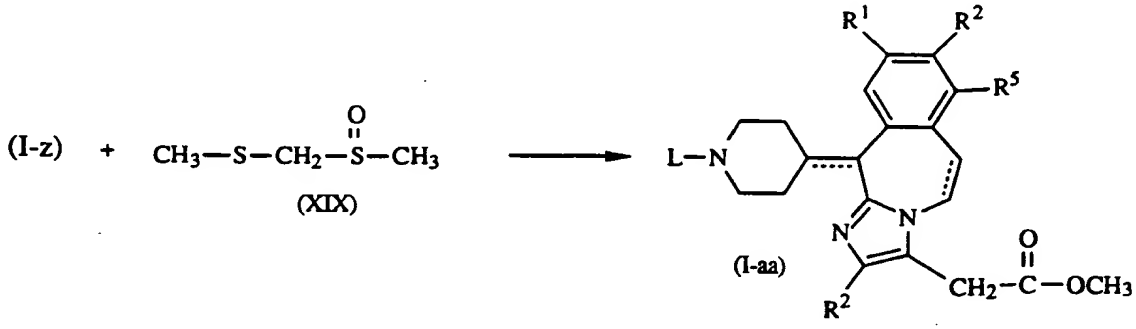
The compounds of formula (I) wherein R^3 is C_{1-4}alkyloxycarbonylethenyl, said compounds being represented by the formula (I-y), can be prepared by reacting a compound of formula (I) wherein R^3 is formyl, said compounds being represented by the formula (I-z) with a reagent of formula (XVIII) in the presence of a base e.g. piperidine, pyridine, and the like.



The compounds of formula (I-y) can be further hydrolyzed into a compound of formula (I) wherein R^3 is hydroxycarbonylethenyl, in the presence of an acid or a base.

The compounds of formula (I) wherein R^3 is methoxycarbonylmethyl, said compounds being represented by the formula (I-aa), can be prepared by reacting a

compound of formula (I-z) with a reagent of formula (XIX) in the presence of benzyltrimethyl ammonium hydroxide in a reaction-inert solvent e.g. tetrahydrofuran.



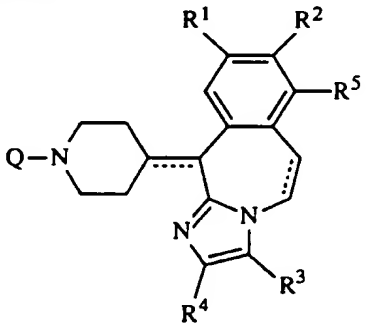
The compounds of formula (I-aa) can be further hydrolyzed into a compound of formula (I) wherein R^3 is hydroxycarbonylmethyl, in the presence of an acid or a base.

The compounds of formula (I) may further be converted into each other following art-known functional group transformation procedures.

For example, the compounds of formula (I) wherein L contains a C_{1-4}alkyloxycarbonyl moiety can be hydrolyzed into a compound of formula (I) wherein L contains a hydroxycarbonyl moiety in the presence of an acid or a base.

The compounds of formula (I) wherein L is C_{1-4}alkyloxyphenylC_{1-6}alkyl can be converted into a compound of formula (I) wherein L is hydroxyphenylC_{1-6}alkyl upon treatment with an acid, such as, for example, hydrobromic acid, hydroiodic acid or a Lewis acid, e.g. borontrifluoride, aluminiumtrichloride and the like.

The compounds of formula (VII-a to VII-g) intervening in the preparations described hereinbefore are novel and have especially been developed for use as intermediates in said preparations. Consequently, the present invention also relates to novel compounds of formula



(VII)

the addition salt forms thereof and the stereochemically isomeric forms thereof, wherein each of the dotted lines independently represents an optional bond,

R^1, R^2, R^3, R^4 and R^5 are as defined under formula (I); and

Q is (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with halo, cyano, amino, isothiocyanato, (4-amino-3-pyridinyl)aminothiocarbonyl-amino, $(CH_3O)_2CH-CH_2-NH-C(=NCH_3)-NH-$ or methylsulfonyloxy; provided that 1-acetyl-4-(5,6-dihydro-11H-imidazol[1,2-b][3]benzazepine-11-ylidene)piperidine is excluded.

Particularly interesting compounds of formula (VII) are those wherein Q represents (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino, the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof.

In the following paragraphs there are described several methods of preparing the starting materials employed in the foregoing preparations.

The intermediates of formula (II) can be prepared from the corresponding ketones of formula (III) by reduction.

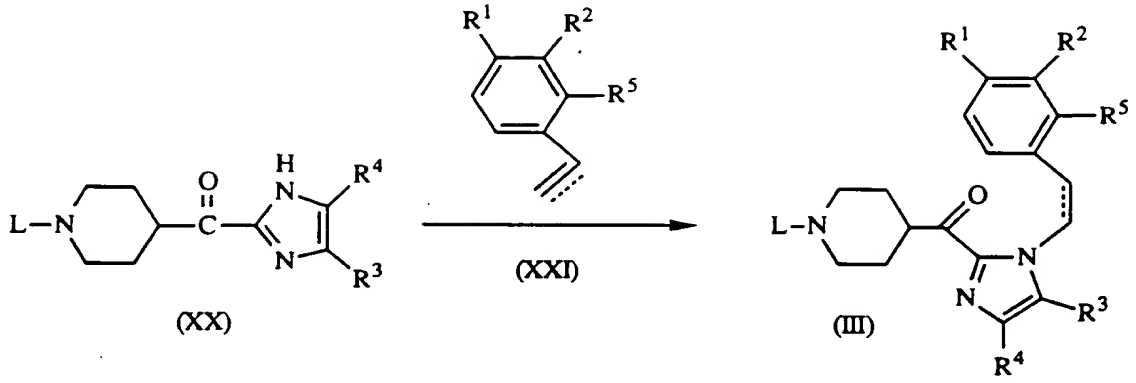
(III) $\xrightarrow{\text{reduction}}$ (II)

Said reduction can conveniently be conducted by reacting the starting ketone (III) with hydrogen in a solvent such as, for example, an alcohol, e.g. methanol, ethanol; an acid, e.g. acetic acid; an ester, e.g. ethyl acetate; in the presence of a hydrogenation catalyst, e.g. palladium-on-charcoal, platinum-on-charcoal, Raney Nickel.

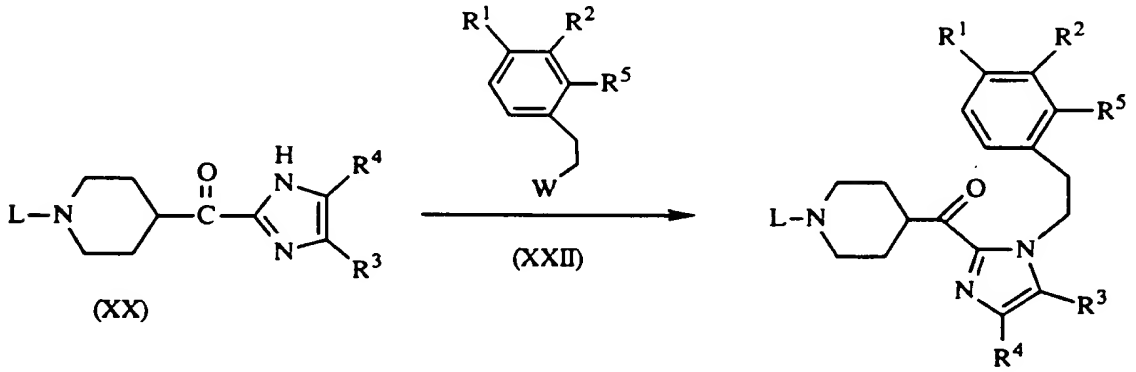
In order to enhance the rate of the reaction, the reaction mixture may be heated and, if desired, the pressure of the hydrogen gas may be raised.

Alternatively, the alcohols of formula (II) can also be prepared by reducing the ketones (III) with a reducing agent such as, for example, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride and the like in a suitable solvent such as, for example, an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran and the like; an alcohol, e.g. methanol, ethanol and the like.

The ketones of formula (III) can be prepared by the addition of a compound of formula (XX) to a reagent of formula (XXI) under the reaction conditions described hereinbefore for the preparation of the compounds of formula (I-g) from the compounds of formula (I-c).



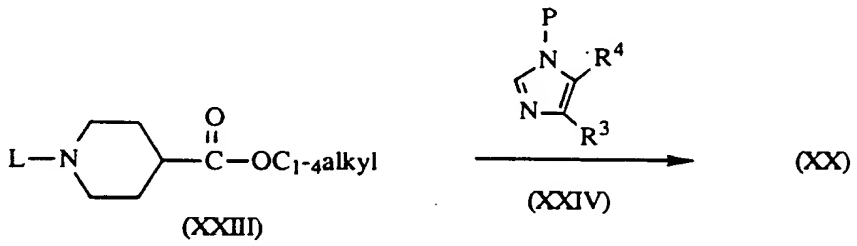
The ketones of formula (III) wherein the dotted line is not an optional bond can be prepared by N-alkylating an intermediate of formula (XX) with a reagent of formula (XXII) wherein W represents a reactive leaving group as defined hereinbefore.



Said N-alkylation reaction can conveniently be conducted following the procedures employed in preparing the compounds of formula (I-e) from the compounds of formula (I-c).

Further, the ketones of formula (III) wherein the dotted line is not an optional bond may also be prepared by reductive N-alkylation of the compounds of formula (XX) under the reaction conditions described for the preparation of the compounds of formula (I-f) from the compounds of formula (I-c).

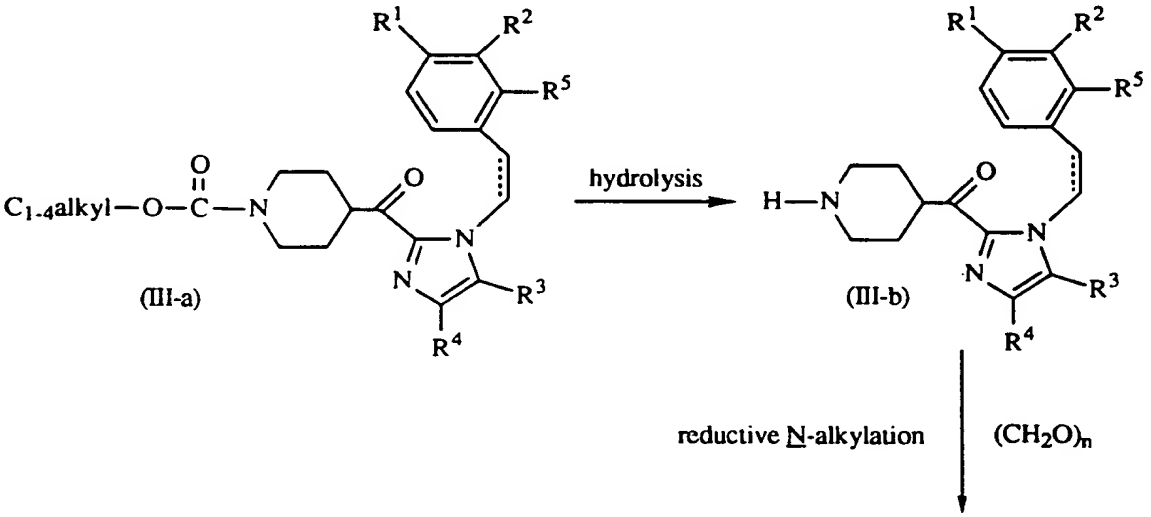
The intermediates of formula (XX) are conveniently prepared from an ester of formula (XXIII) by reaction with a protected imidazole derivative of formula (XXIV) by reaction with a strong base such as, for example, methyl lithium, butyl lithium, sodium amide, a dialkyl lithium amide, e.g. diisopropyl lithium amide, or a mixture thereof, in a reaction-inert solvent, e.g. tetrahydrofuran, hexane, methylbenzene and the like, or a mixture thereof.

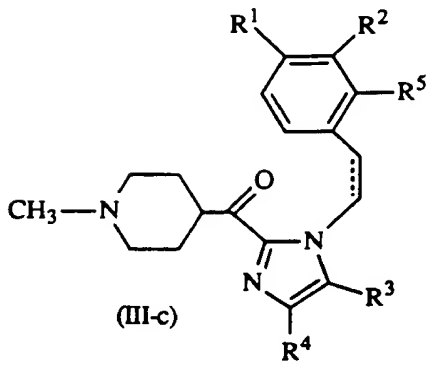


In (XXIV) P represents a protective group such as, for example, di(C_{1-4}alkoxy)-methyl, C_{1-4}alkoxymethyl, benzenesulfonyl, trimethylsilylethoxymethyl, N,N-dialkyl-aminomethyl which can be removed by acid hydrolysis. The reaction of (XXIII) and (XXIV) is conveniently conducted at low temperatures. For example, the reagent (XXIV) may be added at a temperature between about -80°C to about -40°C to the strong base. Subsequently, the ester (XXIII) is added and the reaction mixture is allowed to warm up gently to room temperature. The thus obtained product is converted into intermediate (XX) by very mild acid hydrolysis and isolated in a conventional manner.

The ketones of formula (III) wherein L represents methyl, can be prepared from the ketones wherein L represents hydrogen by reductive N-alkylation with formaldehyde following the methods described hereinbefore for the preparation of the compounds of formula (I-f) from the compounds of formula (I-c).

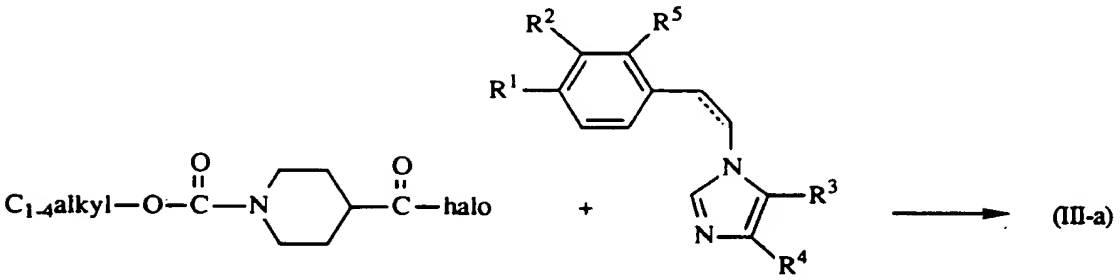
The ketones of formula (III) wherein L represents hydrogen are prepared by hydrolysis of a carbamate of formula (III-a) in acidic or basic media following conventional methods as described hereinbefore for the preparation of compounds of formula (I-c) from the compounds of formula (I-b).





(III-c)

The intermediates of formula (III-a) can be prepared by reacting an acid halide of formula (XXV) with an imidazole derivative of formula (XXVI).

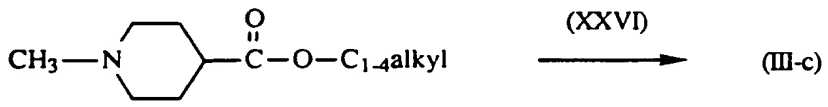


(XXV) (XXVI) (III-a)

Said reaction is conveniently conducted by stirring and heating the reactants in the presence of a base such as, for example, an amine, e.g. N,N-diethylethanamine, N-methylmorpholine and the like, in a suitable solvent such as, for example, pyridine, acetonitrile or a mixture thereof.

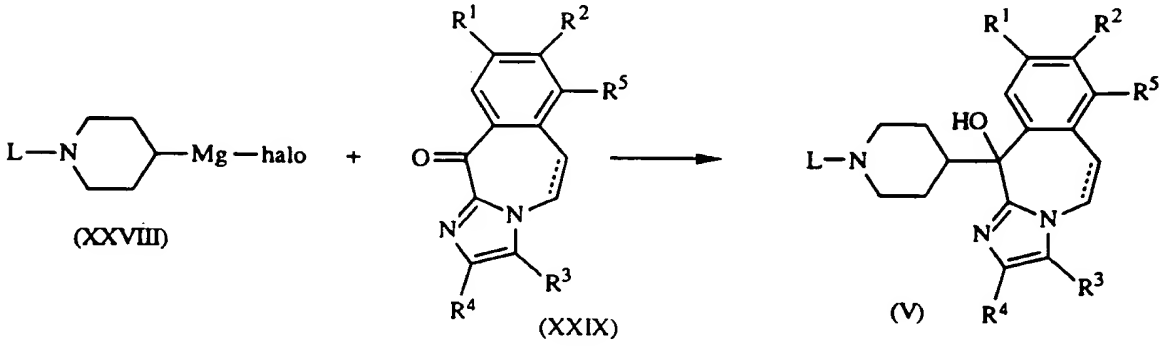
The intermediates of formula (III-c) can also be prepared from an ester of formula (XXVII) by reaction with an imidazole of formula (XXVI) in the presence of a strong base such as, for example, methyl lithium, butyl lithium, sodium amide, a dialkyl lithium amide, e.g. diisopropyl lithium amide, or a mixture thereof, in a suitable reaction-inert solvent, e.g. tetrahydrofuran, hexane, methylbenzene and the like, or a mixture thereof.

Said reaction is conveniently conducted at low temperatures. For example the reagent (XVI) may be added at a temperature between about -80°C to about -40°C to the strong base. Subsequently the ester is added and the reaction mixture is allowed to warm up gently to room temperature.



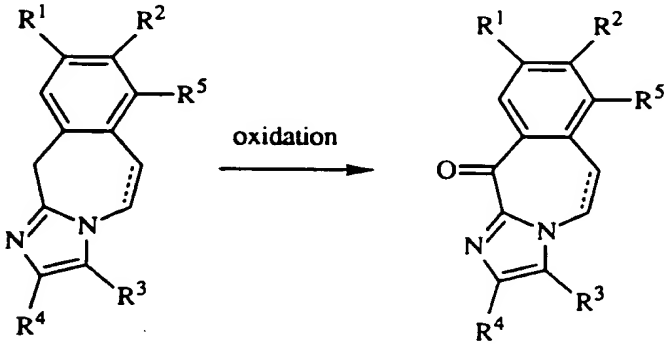
(XXVII) (III-c)

The intermediates of formula (V) can be prepared by addition of a Grignard reagent (XXVIII) to a ketone of formula (XXIX) in a reaction-inert solvent, e.g. tetrahydrofuran.



(XXVIII) (XXIX) (V)

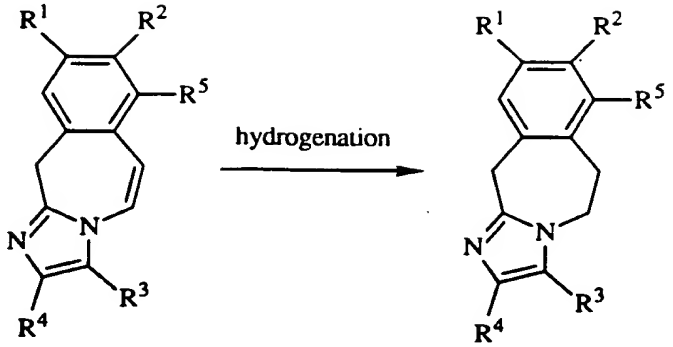
The tricyclic ketones of formula (XXIX) in turn are prepared from intermediates of formula (XXX) by oxidation with suitable oxidizing reagent in a reaction-inert solvent.



(XXX) (XXIX)

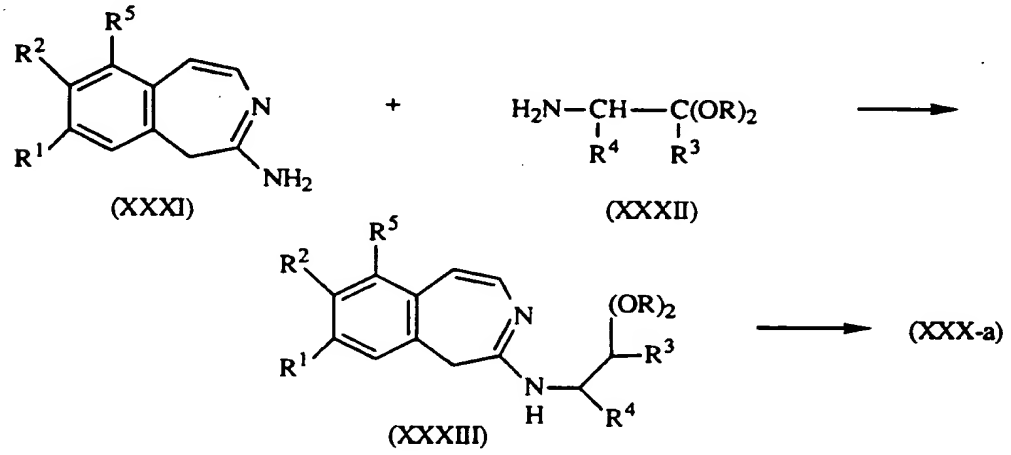
Suitable oxidizing reagents are, for example, manganese dioxide, selenium dioxide, ceric ammonium nitrate and the like. Reaction-inert solvents are, for example, halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like.

The compounds of formula (XXX) wherein the dotted lines do not represent an optional bond, can be prepared from the corresponding compounds of formula (XXX) wherein said dotted lines do represent an optional bond, following art-known hydrogenation procedures, e.g. by reaction with hydrogen in the presence of a hydrogenation catalyst.



(XXX-a) (XXX-b)

The intermediates of formula (XXX-a) can be prepared from a benzazepine of formula (XXXI) by reaction with a reagent of formula (XXXII) and cyclization of the thus obtained intermediate (XXXIII) in an acidic medium. In (XXXII) R represents C_{1-4}alkyl or both radicals R taken together represent C_{2-6}alkanediyl, e.g. 1,2-ethanediyl, 1,3-propanediyl, 2,2-dimethyl-1,3-propanediyl.

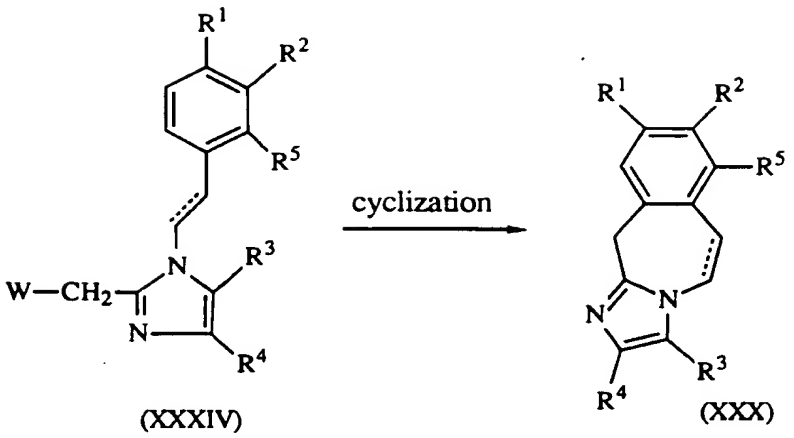


(XXXI) (XXXII) (XXXIII) (XXX-a)

The preparation of (XXXIII) is conveniently conducted by stirring and heating the reactants in a reaction-inert solvent such as, for example, an alcohol, e.g. methanol, ethanol and the like.

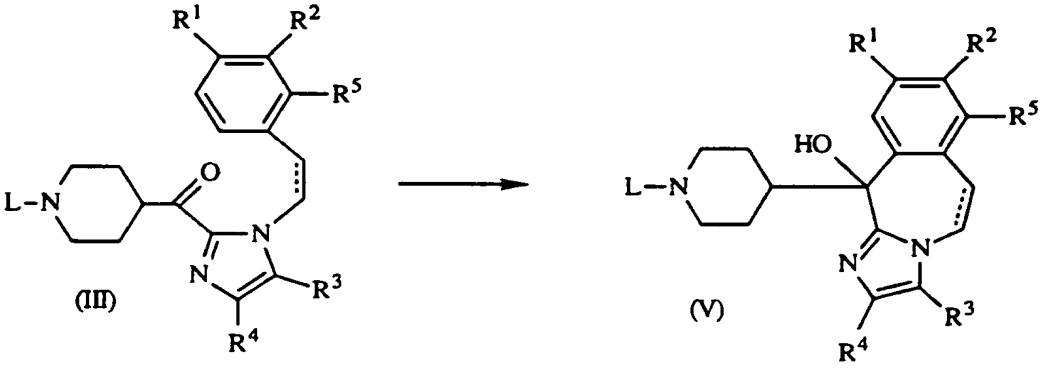
The cyclization reaction to the intermediates of formula (XXX-a) is conducted by stirring and heating the starting material (XXXIII) in a carboxylic acid such as, for example, acetic acid, propanoic acid, optionally in admixture with a mineral acid such as, for example, hydrochloric acid.

The intermediates of formula (XXX) can also be prepared from cyclization of an intermediate of formula (XXXIV).



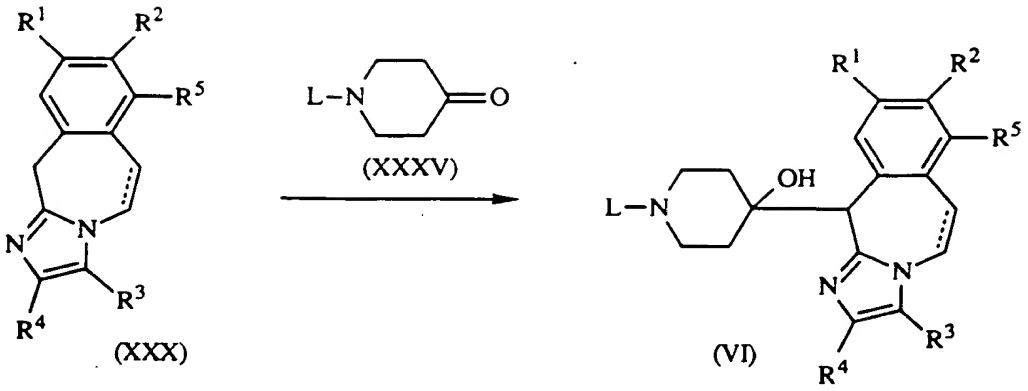
Said cyclization reaction is conveniently conducted in the presence of a Lewis acid, e.g. aluminium chloride, and the like. In some instances it may be appropriate to supplement the reaction mixture with a suitable amount of sodium chloride.

The intermediates of formula (V) can also be prepared from the cyclization of an intermediate of formula (III) in the presence of an acid in a reaction inert solvent.

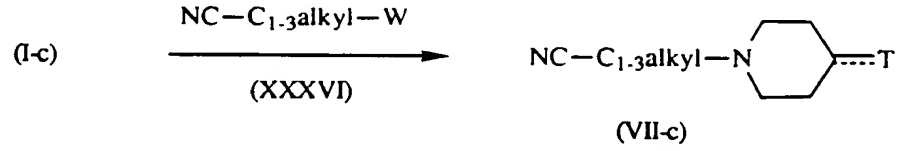


An appropriate acid in the above reaction is, for example, a Lewis acid, e.g. tin(IV)chloride and the like. A suitable reaction-inert solvent is, for example, a halogenated hydrocarbon, e.g. dichloromethane, 1,2-dichloroethane, and the like.

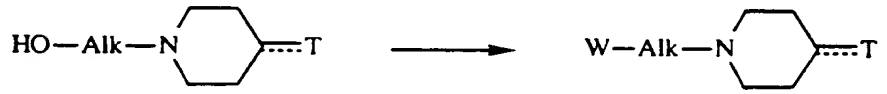
The intermediates of formula (VI) can be prepared by reaction of a ketone of formula (XXXV) with an intermediate of formula (XXX) in the precence of e.g. lithium diisopropylamide in a reaction-inert solvent, e.g. tetrahydrofuran.



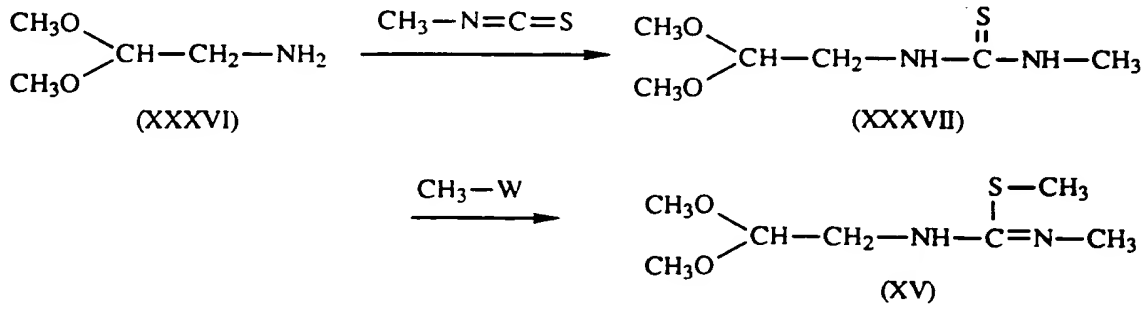
The intermediates of formula (VII-c) can be prepared by N-alkylating a compound of formula (I-c) with a reagent of formula (XXXVI) following the procedures described hereinbefore for the preparation of the compounds of formula (I-e).



The intermediates of formula (VII-d) can be prepared from the compounds of formula (I-k) wherein Y is oxygen by reaction with a halogenating reagent such as, for example, thionyl chloride, phosphorous trichloride, phosphoryl chloride and the like, or by reaction with a sulfonating reagent such as, for example, methanesulfonyl chloride, 4-methylbenzenesulfonyl chloride and the like.

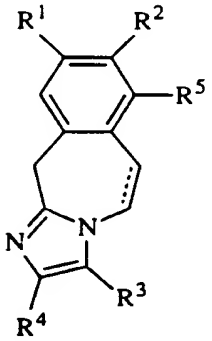


The intermediates of formula (XV) can be prepared by the following reaction sequence.



The reaction of (XXXVI) with the isothiocyanate reagent can conveniently be conducted in a reaction-inert solvent such as, for example, an ether, e.g. tetrahydrofuran and the like. The resulting intermediate of formula (XXXVII) is methylated in a reaction-inert solvent such as, for example, a ketone, e.g. 2-propanone and the like.

The compounds of formula (XXX) intervening in the preparations described hereinbefore are novel, except for 2-methylimidazo[2,1-b][3]benzazepine, 2-phenylimidazo[2,1-b][3]benzazepine and 8,9-dimethoxyimidazo[2,1-b][3]benzazepine and have especially been developed for use as intermediates in said preparations. Consequently, the present invention also relates to novel compounds of formula



(XXX)

the addition salt forms thereof and the stereochemically isomeric forms thereof, wherein R^1, R^2, R^3, R^4, and R^5 are as defined under formula (I), 2-methylimidazo[2,1-b][3]benzazepine, 2-phenylimidazo[2,1-b][3]benzazepine and 8,9-dimethoxyimidazo[2,1-b][3]benzazepine being excluded.

The compounds of formula (I) and some of the compounds of formula (VII), in particular those wherein Q is (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof possess useful pharmacological properties. In particular they are active antiallergic agents, which activity can clearly be demonstrated by he test results obtained in a number of indicative tests.

Antihistaminic activity can be demonstrated in
'Protection of Rats from Compound 48/80 - induced Lethality' test (Arch. Int. Pharmacodyn. Ther., 234, 164-176, 1978);
'Histamine - induced Lethality in Guinea Pigs' test (Arch. Int. Pharmacodyn. Ther., 251, 39-51, 1981);
and the broad antiallergic activity can be demonstrated in
'Passive cutaneous anaphylaxis in Rats' test (Drug Dev. Res., 5, 137-145, 1985) (For some compounds this test has been modified by replacing compound 48/80 by Ascaris

allergens) and the
'Ascaris Allergy in Dogs' test (Arch. Int. Pharmacodyn. Ther., 251, 39-51, 1981 and Drug Dev. Res., 8, 95-102, 1986).

The compounds of the present invention show a broad spectrum antiallergic profile as is evidenced by the results obtained in the diversity of test procedures cited hereinbefore.

A second advantageous feature of the compounds of the present invention resides in their excellent oral activity; the present compounds when administered orally have been found to be practically equipotent with the same being administered subcutaneously.

A particularly important asset of most of the present compounds is their lack of sedating properties at therapeutic dose levels, a troublesome side effect associated with many antihistaminic and antiallergic compounds. The non-sedating properties of the present compounds can be demonstrated, for example, by the results obtained in studying the sleep - wakefulness cycle of the rat (Psychopharmacology, 97, 436-442, (1989)).

Another interesting feature of the present compounds relates to their fast onset of action and the favorable duration of their action.

In view of their antiallergic properties, the compounds of formula (I) and (VII), wherein Q is (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino, and their acid addition salts are very useful in the treatment of broad range of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, allergic asthma and the like.

In view of their useful antiallergic properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the antiallergic compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups,

elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid addition salts of the subject compounds due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present invention also relates to a method of treating warm-blooded animals suffering from said allergic diseases by administering to said warm-blooded animals an effective antiallergic amount of a compound of formula (I) and (VII), wherein Q is (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino or a pharmaceutically acceptable acid addition salt form thereof.

In general it is contemplated that an effective antiallergic amount would be from about 0.001 mg/kg to about 20 mg/kg body weight, and more preferably from about 0.01 mg/kg to about 5 mg/kg body weight.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects.

Experimental part

A. Preparation of the intermediates

Example 1

a) To a cooled mixture of 54.2 g of 1-(2-phenylethyl)-1H-imidazole, 34.7 g of N,N-diethylethanamine and 50 ml of pyridine there were added dropwise 69.2 g of ethyl 4-chlorocarbonyl-1-piperidinecarboxylate(temp. ≤.20 °C) and then 30 ml of acetonitrile. The whole was stirred for 2 hours at room temperature and for 4 hours at reflux temperature. After cooling, there were added 30 ml NaOH 50% and refluxing was continued for 1/2 hour. The cooled reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 97:3). The eluent of the desired fraction was evaporated and the residue was dried, yielding 38 g (33.9 %) of ethyl 4-[[1-(2-phenylethyl)-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 1).

In a similar manner there was also prepared :

ethyl 4-[[1-[2-(2-chlorophenyl)ethyl]-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 37).

b) A mixture of 9 g of intermediate (1) and 50 ml of hydrobromic acid 48% was stirred for 5 hours at 80°C. The reaction mixture was evaporated and the residue was boiled in 2-propanol. After cooling, the precipitate was filtered off and dried, yielding 10.85 g (97.5%) of [1-(2-phenylethyl)-1H-imidazol-2-yl] (4-piperidinyl)methanone dihydrobromide; mp. 275.3 °C (interm. 2).

In a similar manner there was also prepared :

[1-[2-(2-methylphenyl)ethyl]-1H-imidazol-2-yl](4-piperidinyl)methanone dihydrobromide hemihydrate; mp. 231.7°C (interm. 38).

c) A mixture of 55 g of intermediate (2), 70 ml of formaldehyde and 70 ml of formic acid was stirred for 5 hours at reflux temperature. After cooling, the reaction mixture was diluted with water and basified with NaOH(aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was dried, yielding 30 g (82.0%) of (1-methyl-4-piperidinyl) [1-(2-phenylethyl)-1H-imidazol-2-yl]methanone (interm. 3).

In a similar manner there were also prepared :

[1-[2-(4-fluorophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidinyl)methanone (interm. 4); and
[1-[2-(2-chlorophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidinyl)methanone (interm. 39).

Example 2

A mixture of 70.6 g of intermediate (2) and 700 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 2 g of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 54 g (75.7 %) of α-[1-(2-phenylethyl)-1H-imidazol-2-yl]-4-piperidinemethanol; mp. 144.6 °C (interm. 5).

Example 3

a) A mixture of 28.9 g of 2-(4-methylphenyl)ethanol methanesulfonate, 18.6 g of 1H-imidazole, 22.7 g of potassium carbonate and 600 ml of tetrahydrofuran was stirred for 18 hours at reflux temperature. After cooling, the reaction mixture was evaporated and the residue was taken up in water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was destilled (13.3 Pa; 120 °C), yielding 20.1 g (83.0%) of 1-[2-(4-methylphenyl)ethyl]-1H-imidazole (interm. 6).
In a similar manner there were also prepared :
1-[2-(3-methylphenyl)ethyl]-1H-imidazole; bp. 120°C at 13.3 Pa (interm. 7),
1-[2-(4-bromophenyl)ethyl]-1H-imidazole (interm. 8), and
1-[2-(3-chlorophenyl)ethyl]-1H-imidazole; bp. 134°C at 13.3 Pa (interm. 9).

b) A mixture of 67 g of 1-(2-chloroethyl)-3-methoxybenzene, 53.1 g of 1H-imidazole, 99 g of sodium carbonate, 500 ml of 4-methyl-2-pentanone and a few crystals of potassium iodide was stirred for 48 hours at reflux temperature. After cooling, the reaction mixture was diluted with water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was destilled (13.3 Pa; 160 °C), yielding 49.5 g (62.8%) of 1-[2-(3-methoxyphenyl)ethyl]-1H-imidazole (interm. 10).

Example 4

a) To a stirred amount of 250 ml of N,N-dimethylformamide under nitrogen, there were added portionwise 6 g of a dispersion of sodium hydride in mineral oil and 82.1 g of 4-methylimidazole and then dropwise 132 g of phenylxirane. The whole was stirred for 50 hours and then diluted with 1000 ml of water. The precipitate was filtered off,

washed with water and 2,2'-oxybispropane and recrystallized from a mixture of acetonitrile and ethanol. The product was filtered off and dried, yielding 58.1 parts (28.7%) of 5-methyl-α-phenyl-1H-imidazole-1-ethanol; mp. 192.7 °C (interm. 11).

b) A mixture of 57.1 g of intermediate (11), 130 ml of 2-propanol saturated with HCl and 500 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 5 g of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was diluted with water and the whole was basified with NaOH(aq.). The product was extracted with dichloromethane and the extracted was dried, filtered and evaporated. The residue was co-evaporated with methylbenzene (3x), yielding 52.9 g (100%) of 5-methyl-1-(2-phenylethyl)-1H-imidazole (interm. 12).

In a similar manner there was also prepared :

1-[2-(2-methylphenyl)ethyl]-1H-imidazole (interm. 49).

Example 5

a) To a cooled mixture (ice-bath) of 10.1 g of intermediate (10), 12 g of N,N-diethylethanamine and 150 ml of acetonitrile there were added dropwise 21.95 g of ethyl 4-chlorocarbonyl-1-piperidinecarboxylate, keeping the temperature below 20 °C. After stirring for 2 hours at room temperature and 4 hours at reflux temperature, there were added dropwise 10 ml NaOH. The whole was refluxed for 1/2 hour, cooled and evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 22 g (100%) of ethyl 4-[[1-[2-(3-methoxyphenyl)ethyl]-1H-imidazol-2-yl]-carbonyl]-1-piperidinecarboxylate (interm. 13).

In a similar manner there were also prepared :

ethyl 4-[[1-[2-(3-chlorophenyl)ethyl]-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 14),

1-acetyl-4-[[1-[2-(4-methylphenyl)ethyl]-1H-imidazol-2-yl]carbonyl]piperidine (interm. 15),

ethyl 4-[[5-methyl-1-(2-phenylethyl)-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 16),

ethyl 4-[[1-[2-(3-methylphenyl)ethyl]-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 17),

ethyl 4-[[1-[2-(4-bromophenyl)ethyl]-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 18), and

ethyl 4-[[1-[2-(2-methylphenyl)ethyl]-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 40).

b) A mixture of 4.4 g of intermediate (13) and 120 ml of hydrochloric acid 12N was stirred for 72 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water, basified with NaOH and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / $CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated, yielding 2.63 g (83.9 %) of [1-[2-(3-methoxyphenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone (interm. 19).

In a similar manner there were also prepared :

[1-[2-(4-methylphenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone dihydrochloride (interm. 20),

[1-[2-(3-chlorophenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone (interm. 21), and

[1-[2-(2-methylphenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone dihydrobromide; mp. 268.1°C (interm. 41).

c) A mixture of 130 g of intermediate (16) and 1000 ml of hydrobromic acid 48% was stirred for 24 hours at 80 °C. The reaction mixture was evaporated and the residue was recrystallized from 2-propanol. After cooling, the precipitate was filtered off and dried, yielding 124.2 g (95.6%) of [5-methyl-1-(2-phenylethyl)-1H-imidazol-2-yl] (4-piperidinyl)methanone dihydrobromide (interm. 22).

In a similar manner there were also prepared :

[1-[2-(3-methylphenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone dihydrobromide (interm. 23), and

[1-[2-(4-bromophenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone dihydrobromide hemihydrate (interm. 24).

Example 6

A mixture of 5.24 g of intermediate (24), 2 g of polyoxymethylene, 3 g of potassium acetate, 2 ml of a solution of thiophene in methanol 4% and 150 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 2 g of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in water and the whole was basified with K_2CO_3. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated, yielding 3.2 g (85.0%) of [1-[2-(4-bromophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidinyl)-methanone (interm. 25).

In a similar manner there were also prepared :

[1-[2-(3-chlorophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidinyl)methanone (interm. 26), and
[1-[2-(3-methoxyphenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidinyl)methanone (interm. 27).

Example 7

a) A mixture of 3.16 g of 1H-3-benzazepin-2-amine, 4.17 g of 2,2-dimethoxy-ethanamine and 50 ml of methanol was stirred for 16 hours at reflux temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in hexane. The precipitate was filtered off, yielding 4.9 g (100%) of N-(2,2-dimethoxyethyl)-1H-3-benzazepin-2-amine (interm. 28).

b) A mixture of 4.9 g of intermediate (28), 70 ml of acetic acid and 9 ml of hydrochloric acid 36% was stirred for 18 hours at 70°C. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NaOH(aq.) and extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was treated with active charcoal in 1,1'-oxybisethane. The whole was filtered and the filtrate was evaporated. The residue was triturated in hexane. The product was filtered off and dried, yielding 1.04 g (28.5%) of 11H-imidazo[2,1-b][3]benzazepine; mp. 85.5 °C (interm. 29).

c) A mixture of 5 g of intermediate (29), 20 g of manganese dioxide and 150 ml of trichloromethane was stirred for 50 hours at reflux temperature. The whole was filtered over diatomaceous earth, 20 g of manganese dioxide were added and refluxing was continued for 48 hours (2x). The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was triturated in 1,1'-oxybisethane and then boiled in acetonitrile. After cooling, the product was filtered off and dried, yielding 2.61 g (53.2%) of 11H-imidazo-[2,1-b][3]benzazepin-11-one; mp. 218.9 °C (interm. 30).

d) A mixture of 10 ml of tetrahydrofuran and 1.24 g of magnesium was stirred under a nitrogen atmosphere. 1 Crystal of iodine and then dropwise 1.2 g of bromoethane were added and at reflux tempereature there was added a solution of 6.7 g of 4-chloro-1-methylpiperidine in 25 ml of tetrahydrofuran. After refluxing for 1 hour, the reaction mixture was cooled (0 °C). Then there were added 25 ml of tetrahydrofuran and portionwise 9.8 parts of intermediate (30), keeping the temperature below 10 °C. The whole

was stirred for 1 hour at room temperature and decomposed with NH_4Cl (aq.). The product was extracted with trichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH (NH_3) 95:5). The eluent of the second fraction was evaporated and the residue was crystallized from acetonitrile in 2 fractions, yielding 4.76 parts (32.2%) of 11-(1-methyl-4-piperidinyl)-11H-imidazo[2,1-b][3]benzazepin-11-ol; mp. 155.2 °C (interm. 31).

Example 8

Following the procedure of example 10 (c) and (d) 2-phenyl-11H-imidazo[2,1-b][3] benzazepine-11-one was converted into 11-(1-methyl-4-piperidinyl)-2-phenyl-11H-imidazo[2,1-b][3]benzazepin-11-ol; mp. 239.8 °C (interm. 32).

A mixture of 6 g of intermediate (32) and 300 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 3 g of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 3.2 g (53.5%) of 6,11-dihydro-11-(1-methyl-4-piperidinyl)-2-phenyl-5H-imidazo[2,1-b][3]benzazepin-11-ol; mp. 225.3 °C (interm. 33).

Example 9

a) To a cooled (0°C) mixture of 46.2 g of 3-fluorobenzenethanol, 40 ml of N,N-diethylethanamine and 500 ml of dichloromethane, there were added dropwise 41.2 g of methanesulfonyl chloride, keeping the temperature below 5°C. After stirring for 18 hours at room temperature, the reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 81 g (100%) of 2-(3-fluorophenyl)ethanol methanesulfonate (ester) (interm. 34).

b) A mixture of 72 g of intermediate (34), 45 g of 1H-imidazole, 55.5 g of potassium carbonate and 1000 ml of tetrahydrofuran was stirred over weekend at reflux temperature. The reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of

the desired fraction was evaporated and the residue was distilled (53.2 Pa; 130 °C), yielding 37.8 parts (60.2%) of 1-[2-(3-fluorophenyl)ethyl]-1H-imidazole (interm. 35).

c) To a cooled (-70 °C) mixture of 5.5 g of 2-methyl-N-(1-methylethyl)ethanamine and 100 ml of tetrahydrofuran under a nitrogen atmosphere there were added dropwise 22 ml of butyllithium and after stirring for 15 min. at -40 °C, 9.5 g of intermediate (35) at -70°C. Stirring at -70 °C was continued for 1 hour and then there were added 9.4 g of ethyl 1-methyl-4-piperidinecarboxylate. The whole was stirred for 18 hours at room temperature, decomposed with water and evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → CH_2Cl_2 / CH_3OH 80:20). The eluent of the desired fraction was evaporated, yielding 8 g (50.7%) of [1-[2-(3-fluorophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidinyl)methanone (interm. 36).

Example 10

a) To a stirred and cooled (-70°C) mixture of 18.8 g of N-(1-methylethyl)-2-propanamine in 200 ml of tetrahydrofuran (under nitrogen atmosphere) were added portionwise 42 ml of butyllithium 2.5M in hexane. The mixture was brought to -40°C and stirred at this temperature for 15 minutes. The mixture was cooled again to -70°C and a solution of 17 g of 1-(diethoxymethyl)-1H-imidazole in tetrahydrofuran was added dropwise at this temperature. Stirring was continued for 1 hour and a solution of 18.8 g of ethyl 1-methyl-4-piperidinecarboxylate in 200 ml of tetrahydrofuran was added. After stirring for 1 hour at -70°C and for another hour at room temperature, the mixture was decomposed with water, acidified with HCl and evaporated. The residue was taken up in water, alkalized with potassium carbonate and extracted with a mixture of dichloromethane and methanol. The extract was dried, filtered and evaporated. The residue was purified on silica (eluent : CH_2Cl_2/(CH_3OH/NH_3) 95/5). The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding : 2.75 g of (1H-imidazol-2-yl)(1-methyl-4-piperidinyl)methanone (12.9%); mp. 143.6°C (interm. 42).

b) To 200 ml of N,N-dimethylformamide were added portionwise 13.2 g of a sodium hydride dispersion 50% in mineral oil and then 48.3 g of intermediate (42) under nitrogen atmosphere while stirring. After stirring for 1.5 hours at room temperature, a solution of 65 g of 2-fluorobenzeneethanol methanesulfonate (ester) in N,N-dimethylformamide was added dropwise to the reaction mixture. The reaction mixture was stirred for 18 hours at 60°C, cooled and decomposed with water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was

taken up in water, acidified with hydrochloric acid, washed twice with 2,2'-oxybis-propane, treated with potassium carbonate and extracted again with dichloromethane. The extract was dried, filtered and evaporated. The residue was converted into the (E)-2-butenedioate salt in ethanol. The salt was filtered off and dried, yielding 61.9 g (50.6%) of [1-[2-(2-fluorophenyl)ethyl]-1H-imidazol-2-yl](1-methyl-4-piperidinyl)methanone (E)-2-butenedioate (2:3); mp. 131.7°C (interm. 43).

Example 11

22.3 g of methyl 4'-methyl-(1,1'biphenyl)-2-carboxylate were dissolved in 900 ml of tetrachloromethane under a nitrogen flow. Then there were added 17.8 g of 1-bromo-2,5-pyrrolidinedione and a catalytic amount of dibenzoyl peroxide. After stirring for 2.5 hours at reflux temperature under a nitrogen atmosphere, the reaction mixture was cooled and filtered. The filtrate was evaporated, yielding > 30 g (100%) of methyl 4'-(bromo-methyl)[1,1'-biphenyl]-2-carboxylate as a crude residue (interm. 44).

Example 12

a) To a freshly prepared sodium methoxide solution, prepared in the usual manner starting from 23 g of sodium and 350 ml of methanol was added a solution of 68 g of 1H-imidazole in 100 ml of methanol. The solvent was evaporated and the residue was taken up in 320 ml of N,N-dimethylformamide. The solvent was removed again till the temperature rose to 125°C. After cooling to 30°C, 185 g of (2-bromoethyl)benzene were added to the residue and the whole was stirred overnight. The reaction mixture was diluted with 1500 ml of water and 230 ml of benzene. The separated aqueous layer was extracted twice with benzene. The combined organic layers were treated with 750 ml of a hydrochloric acid solution 4 N and than basified. The product was extracted with benzene. The extract was dried, filtered and evaporated. The oily residue was distilled in vacuo, yielding 55 g of 1-(2-phenylethyl)-1H-imidazole; bp. 140-145°C at 23.3 Pa (interm. 45).

b) A mixture of 34.5 g of intermediate (45) and 200 ml of formaldehyde 37% in water was stirred and refluxed for 48 hours. After evaporation, the residue was taken up in water and treated with a diluted ammonium hydroxide solution while cooling. The whole was stirred for 30 minutes and extracted with methylbenzene. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (eluent : CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in 2,2'-oxybispropane. The precipitated product was filtered off and dried in vacuo, yielding 29.9 g (73.8%) of 1-(2-phenylethyl)-1H-imidazole-2-methanol; mp. 75.4°C (interm. 46).

c) To 50 ml of thionyl chloride were added portionwise 4 g of intermediate (46). The reaction mixture was stirred and refluxed for 30 minutes. The reaction mixture was evaporated and the residue was stirred in 2,2'-oxybispropane. The precipitated product was filtered off and dried, yielding 4.61 g (89.6%) of 2-(chloromethyl)-1-(2-phenylethyl)-1H-imidazole monohydrochloride; mp. 240.2°C (interm. 47).

d) A mixture of 19.6 g of intermediate 47, 59 g of aluminium chloride and 25.5 g of sodium chloride was stirred for 30 minutes at 100°C. After cooling, the reaction mixture was poured into ice water and treated with sodium hydroxide. The product was extracted with methylbenzene. The extract was dried, filtered and evaporated, yielding 13.1 g (93.5%) of 6,11-dihydro-5H-imidazo[2,1-b][3]benzazepine (interm. 48).

B. Preparation of the final compounds

Example 13

A mixture of 2.5 g of intermediate (26) and 10 ml of trifluoromethanesulfonic acid was stirred for 72 hours at 110°C under nitrogen. After cooling, the reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH (NH_3) 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.95 g (40.4%) of 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine; mp. 186.6°C (comp. 3.10).

Example 14

A mixture of 2 g of intermediate (27) and 10 ml of methanesulfonic acid was stirred for 1 hour at 100°C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 1 g (30.8%) of 6,11-dihydro-8-methoxy-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine (Z)-2-butenedioate(1:2); mp. 190.3°C (comp. 3.01).

Example 15

A mixture of 8 g of intermediate (36), 24 g of aluminum chloride and 10.3 g of sodium chloride was stirred at 140°C until the whole was melted. Stirring was continued for

1 hour at 120°C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → CH_2Cl_2 / $CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was triturated in 2,2'-oxybispropane and recrystallized from 4-methyl-2-pentanone. The product was filtered off and dried, yielding 0.58 g (10.8%) of 8-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine; mp. 152.4°C (comp. 3.15).

Example 16

A mixture of 3.5 g of intermediate (5) and 10 ml of trifluoromethanesulfonic acid was stirred for 18 hours at 110°C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was washed with water, dried, filtered and evaporated. The residue was converted into the (E)-2-butenedioate (1:2) salt in ethanol. The salt was recrystallized from ethanol, yielding 0.8 g (13.3%) of 6,11-dihydro-11-(4-piperidinyl)-5H-imidazo-[2,1-b][3]benzazepine (E)-2-butenedioate (1:2); mp. 220.2°C (comp. 5.01).

Example 17

A mixture of 2.2 g of intermediate (33), 10 ml of sulfuric acid and 10 ml of methanesulfonic acid was stirred for 2 hours at 70°C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → CH_2Cl_2 / $CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.73 g (34.2%) of 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-2-phenyl-5H-imidazo-[2,1-b][3]benzazepine; mp. 171.5°C (comp. 4.01).

Example 18

A mixture of 14.7 g of intermediate (31) and 150 ml of acetic anhydride was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NaOH (aq.) and then extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the first fraction was evaporated and the residue was taken up in 1,1'-oxybisethane. The whole was filtered and the filtrate was treated with

activated charcoal. After filtration, the solution was evaporated and the residue was triturated in 2,2'-oxybispropane. The product was filtered off and dried, yielding 1.6 g (11.5%) of product. The second fraction was also evaporated and the residue taken up in 1,1'-oxybisethane. The whole was filtered and the filtrate was combined with the 2,2'-oxybispropane-filtrate of the first fraction, and evaporated, yielding an additional 8.2 g (59.1%) of product. Total yield : 9.8 g (70.6%) of 11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine; mp. 135.8°C (comp. 6.01).

Example 19

To a stirred and refluxing mixture of 7.2 g of compound (3.10), 4.6 g of N,N-diethylethanamine and 200 ml of methylbenzene there were added dropwise 12.5 g of ethyl chloroformate. After refluxing for 1 hour and subsequent cooling, the reaction mixture was diluted with water. The whole was basified with K_2CO_3 and then extracted with methylbenzene. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 6.62 g (77.4%) of ethyl 4-(8-chloro-5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine-carboxylate; mp. 140.3°C (comp. 3.11).

Example 20

a) A mixture of 2.5 g of compound (1.03) and 50 ml of formaldehyde 40% was stirred for 1 week at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NH_4OH, stirred for 1/2 hour and extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.45 g (16.3%) of ethyl 4-[5,6-dihydro-3-(hydroxymethyl)-11H-imidazo[2,1-b][3]benzazepin-11-ylidene]-1-piperidinecarboxylate; mp. 191.9°C (comp. 4.11).

b) A mixture of 20 g of compound (1.03) and 400 ml of formaldehyde 40% was stirred for 2 weeks at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. After basifying with NH_4OH, the product was extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the third fraction was evaporated, yielding 4.1 g (17.2%) of ethyl 4-[5,6-dihydro-2,3-bis(hydroxymethyl)-11H-imidazo-[2,1-b][3]-

benzazepin-11-ylidene]-1-piperidinecarboxylate (comp. 4.18).

Example 21

A mixture of 13 g of compound (1.03), 13 g of potassium hydroxide and 100 ml of 2-propanol was stirred for 6 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / $CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (1:2) salt in ethanol. The salt was filtered off and dried, yielding 3.52 g (18.3%) of 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine (E)-2-butenedioate (1:2) hemihydrate; mp. 192.5°C (comp. 1.04).

Example 22

A mixture of 60 g of compound (6.02) and 500 ml of hydrobromic acid 48% was stirred for 5 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. After basifying with NaOH (aq.), the product was extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5 → CH_2Cl_2 / $CH_3OH(NH_3)$ 90:10). The eluent of the first fraction was evaporated and the residue was converted into the dihydrobromide salt in ethanol. The salt was filtered off and dried, yielding 27.3 g (37.7%) of 11-(4-piperidinylidene)-11H-imidazo[2,1-b]-[3]benzazepine dihydrobromide hemihydrate; mp. 246.9°C (comp. 6.03).

Example 23

A mixture of 6.1 g of compound (3.11) and 100 ml of hydrochloric acid 12N was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was boiled in 2-propanol. After cooling, the precipitate was filtered off and taken up in water. The whole was basified with NaOH (aq.) and then extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was boiled in acetonitrile. After cooling, the product was filtered off and dried, yielding 2.9 g (59.0%) of 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b]-[3]benzazepine; mp. 197.1°C (comp. 3.12).

Example 24

To a stirred and cooled (ice-bath) mixture of 5.6 g of compound (2.12), 50 ml of dichloromethane and 2.5 g of N,N-diethylethanamine there was added dropwise a

solution of 2.38 g of ethyl chloroformate in 20 ml of dichloromethane. Stirring was continued for 1 hour at room temperature. The reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 2.85 g (40.5%) of ethyl 4-(5,6-dihydro-9-methyl-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinecarboxylate; mp. 156.5°C (comp. 2.13).

Example 25

A mixture of 1.79 g of 3-(2-chloroethyl)-2-oxazolidinone, 2.65 g of compound (1.04), 1.3 g of sodium carbonate, 150 ml of 4-methyl-2-pentanone and 1 g of potassium iodide was stirred for 18 hours at reflux temperature. After cooling, the reaction mixture was diluted with water. The aqueous layer was separated and extracted with dichloromethane. The combined organic layers were dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (2:3) salt in ethanol. The salt was filtered off and dried, yielding 3.4 g (61.5%) of 3-[2-[4-[5,6-dihydro-11H-imidazo[2,1-b] [3]benzazepin-11-ylidene]-1-piperidinyl]ethyl]-2-oxazolidinone (E)-2-butenedioate (2:3); mp. 188.8°C (comp. 1.20).

Example 26

A mixture of 2.3 g of 6-(2-chloroethyl)-7-methylthiazolo[3,2-a]pyrimidin-5-one, 2.65 g of compound (1.04), 1.3 g of sodium carbonate and 100 ml of 4-methyl-2-pentanone was stirred for 24 hours at reflux temperature. After cooling, the reaction mixture was diluted with water. The product was extracted with 4-methyl-2-pentanone and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from 2-propanone. The product was filtered off and dried, yielding 1.89 g (41.3%) of 6-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b]-[3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one; mp. 181.8°C (comp. 1.13).

Example 27

A mixture of 0.83 g of chloroacetonitrile, 2.65 g of compound (1.04), 1.1 g of N,N-diethylethanamine and 80 ml of N,N-dimethylacetamide was stirred for 18 hours at room temperature. The reaction mixture was poured into water and the product was

extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 2.0 g (65.7%) of 4-(5,6-dihydro-11H-imidazo[2,1-b][3]-benzazepin-11-ylidene)-1-piperidineacetonitrile; mp. 220.4°C (comp. 1.26).

Example 28

A mixture of 1.0 g of 3-chloro-2-methyl-1-propene, 2.6 g of compound (1.04), 1.6 g of sodium carbonate and 50 ml of N,N-dimethylacetamide was stirred for 20 hours at 50°C. After cooling, there were added 100 ml of ethyl acetate. The whole was washed with water (3x), dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butene-dioate (2:3) salt in 2-propanol. The salt was filtered off and dried, yielding 2.8 g (56.7%) of 6,11-dihydro-11-[1-(2-methyl-2-propenyl)-4-piperidinylidene]-5H-imidazo[2,1-b] [3]benzazepine (E)-2-butenedioate (2:3); mp. 179.5°C (comp.1.08).

Example 29

A mixture of 1.57 g of 4-chloro-2-methyl-2-butene (dissolved in N,N-dimethylformamide), 2.65 g of compound (1.04), 1.1 g of sodium carbonate, 0.01 g of potassium iodide and 100 ml of N,N-dimethylacetamide was stirred for 18 hours at room temperature. The reaction mixture was poured into water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified twice by column chromatography (silica gel; CH_2Cl_2 / CH_3OH / $CH_3OH(NH_3)$ 90:10:1; HPLC; Lichroprep RP18; CH_3COONH_4 in H_2O 0.5% / CH_3OH / CH_3CN 40:55:5). The eluent of the desired fraction was evaporated and the residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 0.25 g (7.5%) of 6,11-dihydro-11-[1-(3-methyl-2-butenyl)-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine; mp. 127.2°C (comp. 1.09).

Example 30

A mixture of 19 g of compound (2.03), 6 g of chloroacetonitrile, 8 g of N,N-diethylethanamine and 100 ml of N,N-dimethylformamide was stirred for 18 hours at room temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 4.15 g

(19.2%) of 4-(9-fluoro-5,6-dihydro-11H-imidazo[2,1-b][3]-benzazepin-11-ylidene)-1-piperidineacetonitrile; mp. 198.3°C (comp. 2.08).

Example 31

To a stirred mixture of 2.83 g of compound (2.03), 2.12 g of sodium carbonate, 50 ml of N,N-dimethylformamide and 1 g of potassium iodide there were added dropwise 25.4 g of 4-chloro-2-methyl-2-butene (dissolved in N,N-dimethyl-formamide). Stirring at room temperature was continued for 50 hours. The reaction mixture was diluted with water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 2.65 g (45.4%) of 9-fluoro-6,11-dihydro-11-[1-(3-methyl-2-butenyl)-4-piperidinylidene]-5H-imidazo-[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 203.4°C (comp. 2.04).

Example 32

A mixture of 1.5 g of 3-bromo-1-propene, 2.65 g of compound (1.04), 1.0 g of sodium hydrogen carbonate and 100 ml of ethanol was stirred for 5 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with 4-methyl-2-pentanone and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH / $CH_3OH(NH_3)$ 90:10:0 → 90:10:1). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butene-dioate (1:2) salt in 2-propanone. The salt was filtered off and dried for 2 hours in vacuo at 100°C, yielding 1.1 g (20.5%) of 6,11-dihydro-11-[1-(2-propenyl)-4-piperidinylidene]-5H-imidazo-[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 160.8°C (comp. 1.07).

Example 33

A mixture of 2.7 g of compound (3.04), 1 g of polyoxymethylene, 2 ml of a solution of thiophene in methanol 4% and 150 ml of methanol was hydrogenated at normal pressure and 50°C in the presence of 1 g of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (1:2) salt in 2-propanol. The salt was filtered off and dried, yielding 3.1 g (59.0%) of 6,11-dihydro-8-methyl-11-

(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine (E)-2-butenedioate (1:2); mp. 211.0°C (comp. 3.05).

Example 34

A mixture of 2.7 g of compound (5.01), 2 g of polyoxymethylene, 2 ml of a solution of thiophene in methanol 4% and 150 ml of methanol was hydrogenated at normal pressure and room temperature in the presence of 2 g of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was partitioned between dichloromethane and NH_4OH. The aqueous layer was separated and re-extracted with dichloromethane. The combined organic layers were dried, filtered and evaporated. The residue was crystallized from a mixture of 2,2'-oxybispropane and acetonitrile (2x). The product was filtered off and dried, yielding 0.76 g (26.2%) of 6,11-dihydro-11-(1-methyl-4-piperidinyl)-5H-imidazo[2,1-b][3]benzazepine hemihydrate; mp. 117.8°C (comp. 5.02).

Example 35

A mixture of 2.65 g of compound (1.04), 20 ml of acetic acid and 15 ml of 2-propanone was stirred for 2 hours at room temperature under nitrogen. There were added portion-wise 1.5 g of sodium tetrahydroborate and stirring was continued for 18 hours. The reaction mixture was diluted with water and basified with NaOH 15%. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH / $CH_3OH(NH_3)$ 90:10:1). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 2.5 g (46.3%) of 6,11-dihydro-11-[1-(1-methylethyl)-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 183.6°C (comp. 1.06).

Example 36

A mixture of 4 g of compound (4.03), 2 ml of acetic acid, 3 g of sodium acetate and 20 ml of formaldehyde 37% was stirred for 50 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NaOH (aq.) and extracted with a mixture of dichloromethane and methanol. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → CH_2Cl_2 / $CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from a mixture of acetonitrile and 2,2'-oxybispropane. The product was filtered off and dried,

yielding 0.4 g (9.2%) of 6,11-dihydro-3-methyl-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-2-methanol; mp. 166.8°C (comp. 4.21).

Example 37

A mixture of 1.6 g of (2-pyridinyl)ethene, 2.7 g of compound (5.01) and 100 ml of 1-butanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH / CH_3OH:NH_3 90:10:1). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1.7 g (45.6%) of 6,11-dihydro-11-[1-[2-(2-pyridinyl)ethyl]-4-piperidinyl]-5H-imidazo-[2,1-b][3]benzazepine; mp. 170.3°C (comp. 5.04).

Example 38

Through a stirred mixture of 32 g of compound (1.04) and 300 ml of methanol was bubbled gaseous oxirane for 1 hour at room temperature. After stirring for 3 hours at room temperature, the mixture was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH / CH_3OH:NH_3 90:10:0 → 90:10:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in acetonitrile. The salt was filtered off and dried, yielding 15 g (23.1%) of 4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidineethanol (Z)-2-butenedioate(1:2); mp. 145.7°C (comp. 1.30).

Example 39

A solution of 9.6 g of compound (4.08) in 300 ml of methanol/NH_3 was hydrogenated in the presence of 3 g of Raney Nickel catalyst. After complete reaction, the catalyst was filtered off and the filtrate was evaporated, yielding 12.5 g (100%) of 4-(5,6-dihydro-3-methyl-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidineethanamine (comp. 4.09).

Example 40

0.57 g of lithium aluminum hydride were added portionwise to 100 ml of tetrahydrofuran under nitrogen. A solution of 2.3 g of compound (1.26) in tetrahydrofuran was added dropwise and the reaction mixture was stirred for 3 hours at reflux temperature. The mixture was decomposed with 2 ml of water, 2 ml of a sodium hydroxide solution 15%. After filtration over diatomaceous earth, the filtrate was evaporated, yielding 2.3 g (97.5%) of 4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-yl)-1-piperidineethanamine (comp. 5.07).

Example 41

A solution of 3.1 g of compound (1.30) in N,N-dimethylacetamide was added dropwise to a mixture of 0.7 g of a sodium hydride dispersion 50% and 200 ml of N,N-dimethylacetamide under nitrogen and at room temperature. After stirring for 1 hour, 1.1 g of 2-chloropyrimidine were added and the whole was stirred for 16 hours at room temperature. The reaction mixture was decomposed with water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in 2-propanone. The salt was filtered off and dried, yielding 1.4 g (22.6%) of 6,11-dihydro-11-[1-[2-(2-pyrimidinyloxy)ethyl]-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine (Z)-2-butenedioate(1:2); mp. 172.6°C (comp. 1.31).

Example 42

A mixture of 3.3 g of 2-chloropyrimidine, 3.2 g of compound (4.09), 1.26 g of sodium hydrogen carbonate and 200 ml of ethanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 2.56 g (63.9%) of N-[2-[4-(5,6-dihydro-3-methyl-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-2-pyrimidinamine; mp. 171.3°C (comp. 4.10).

Example 43

A mixture of 2.0 g of 5-bromo-1,3,4-thiadiazole-2-amine, 3.42 g of compound (1.27), 1.2 g of sodium carbonate, 0.01 g of potassium iodide and 200 ml of N,N-dimethylacetamide was stirred for 4 hours at 120°C. The reaction mixture was evaporated and the residue was stirred in dichloromethane. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH / CH_3OH:NH_3 90:10:1 → 90:7:3). The eluent of the desired fraction was evaporated and the residue was crystallized from a mixture of acetonitrile and ethanol. The product was filtered off and dried, yielding 1.62 g (36.2%) of N^2-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-1,3,4-thiadiazole-2,5-diamine; mp. 251.4°C (comp. 1.33).

Example 44

To a stirred mixture of 1.1 g of 3-furancarboxyiic acid, 1.9 g of N,N-diethylethanamine and 200 ml of dichloromethane were added portionwise 2.4 g of 2-chloro-1-methyl-pyridinium iodide. After stirring for 1 hour at room temperature, a solution of 2.9 parts of compound (1.27) in dichloromethane was added dropwise. Upon completion, the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was basified with K_2CO_3(aq.) and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 94:6 → 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in 2-propanone. The salt was filtered off and dried, yielding 1.88 g (31.5%) of N-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-ethyl]-3-furancarboxamide (Z)-2-butenedioate(1:2); mp. 202.9°C (comp. 1.35).

Example 45

A mixture of 0.6 g of isocyanatomethane, 3.1 g of compound (1.27) and 100 ml of tetrahydrofuran was stirred for 18 hours at room temperature. The reaction mixture was evaporated and the residue was crystallized from acetonitrile. The precipitated product was filtered off and dried, yielding 2.0 g (54.7%) of N-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-ethyl]-N'-methylurea; mp. 178.1°C (comp. 1.36).

Example 46

a) To a stirred and cooled (-10°C) mixture of 18 g of carbon disulfide, 7.22 g of N,N'-methanetetraylbis[cyclohexanamine] and 150 ml of tetrahydrofuran was added dropwise a solution of 10.8 g of compound (1.27) in tetrahydrofuran. After stirring for 1 hour at room temperature, the reaction mixture was evaporated, yielding 12 g (97.5%) of 6,11-dihydro-11-[1-(2-isothiocyanatoethyl)-4-piperidinylidene]-5H-imidazo[2,1-b]-[3]benzazepine (comp. 1.37).

b) A mixture of 2.7 g of 3,4-pyridinediamine, 8.8 g of compound (1.37) and 150 ml of tetrahydrofuran was stirred for 18 hours at reflux temperature, yielding 11.5 g (100%) of N-(4-amino-3-pyridinyl)-N'-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]thiourea (comp. 1.38).

c) A mixture of 11.5 g of compound (1.38), 7.6 g of mercury(II)oxide, 0.01 g of sulfur and 150 ml of tetrahydrofuran was refluxed for 5 hours. The reaction mixture was filtered while hot over diatomaceous earth and the filtrate was evaporated. The residue

was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH /CH_3OH:NH_3 90:5:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate salt in methanol. The salt was filtered off and dried, yielding 1.65 g (14.4%) of N-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b] [3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-1H-imidazo[4,5-c]pyridin-2-amine (E)-2-butenedioate(1:3) hemihydrate; mp. 203.0°C (comp. 1.39).

Example 47

1 g of gaseous methanamine was bubbled through 100 ml of tetrahydrofuran. A solution of 3.5 g of compound (1.37) in tetrahydrofuran was added and the reaction mixture was stirred for 2 hours at room temperature. After evaporation, the residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH / CH_3OH:NH_3 90:10:0 → 90:10:1). The eluent of the desired fraction was evaporated and the residue was crystallized from 2,2'-oxybispropane. The crystallized product was filtered off and dried, yielding 0.9 g (23.0%) of N-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-N'-methylthiourea hemihydrate; mp. 155.2°C (comp. 1.40).

Example 48

a) A mixture of 7.6 g of compound (1.30) and 100 ml of thionyl chloride was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was stirred in methylbenzene (2x). The obtained residue was dissolved in water and treated with sodium carbonate. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in 2-propanone. The salt was filtered off and dried, yielding 0.7 g (5%) of 11-[1-(2-chloroethyl)-4-piperidinylidene]-6,11-dihydro-5H-imidazo[2,1-b][3]-benzazepine (Z)-2-butenedioate(1:2); mp. 169.9°C (comp. 1.41).

b) A mixture of 2.8 g of 1-methyl-1H-imidazol-2-thiol, 6.5 g of compound (1.41), 8.3 g of potassium carbonate and 200 ml of 2-propanone was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated, the residue was taken up in dichloromethane, washed with water, dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was taken up in methylbenzene and treated with activated charcoal. The whole was filtered while hot, the filtrate was allowed to cool and was then evaporated. The residue was converted into the cyclo-

hexanesulfamate salt in 2-propanone and ethanol. The salt was filtered off and dried, yielding 1.6 g (10.5%) of 6,11-dihydro-11-[1-[2-[(1-methyl-1H-imidazol-2-yl)thio]-ethyl]-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine cyclohexanesulfamate (1:2); mp. 265.4°C (decomp.) (comp. 1.42).

Example 49

a) A mixture of 9.6 g of methyl N-(2,2'-dimethoxyethyl)-N'-methylcarbamimidothioate hydroiodide, 9.3 g of compound (1.27) and 200 ml of 2-propanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated, yielding 17.4 g (100%) of N-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b]-[3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-N'-(2,2-dimethoxyethyl)-N''-methylguanidine monohydroiodide (comp. 1.43).

b) A mixture of 9.3 g of compound (1.43) and 200 ml of a hydrochloric acid solution was stirred for 18 hours at room temperature. The whole was treated with potassium carbonate and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography HPLC (silica gel; $CHCl_3$ / CH_3OH 98:2). The eluent of the desired fraction was evaporated and the residue was converted into the cyclohexanesulfamate salt in 2-propanone and ethanol. The salt was filtered off and dried, yielding 0.71 g (3%) of 4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-N-(1-methyl-1H-imidazol-2-yl)-1-piperidine-ethanamine cyclohexanesulfamate (1:3) dihydrate; mp. 153.9°C (comp. 1.44).

Example 50

A mixture of 1.42 g of 2-mercapto-4-pyrimidinone, 3.1 g of compound (1.27) and 1 ml of N,N-dimethylacetamide was stirred for 4 hours at 140°C. After cooling, the mixture was purified by column chromatography (silica gel; $CHCl_3$ / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the hydrochloride salt in 2-propanone. The salt was filtered off and dried in vacuo, yielding 1.8 g (32.9%) of 2-[[2-[4-(5,6-dihydro-11H-imidazo-[2,1-b][3]-benzazepin-11-ylidene)-1-piperidinyl]ethyl]amino]-4(1H)-pyrimidinone trihydrochloride dihydrate; mp. 234.8°C (comp. 1.45).

Example 51

A mixture of 1 g of compound (4.11), 5 g of manganese(IV)oxide and 100 ml of trichloromethane was stirred for 2 hours at reflux temperature. The reaction mixture was filtered while hot over diatomaceous earth. After evaporation, the residue was purified

by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from 1,1'-oxybis-ethane. The product was filtered off and dried, yielding 0.48 g (48.6%) of ethyl 4-(3-formyl-5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine-carboxylate; mp. 138.2°C (comp. 4.15).

Example 52

To a stirred solution of 9.7 g of compound (4.15) in 100 ml of water was added dropwise a solution of 13.7 g of $AgNO_3$ in 50 ml of water and then a solution of 13.3 g of potassium hydroxide in 50 ml of water. After stirring for 18 hours, the reaction mixture was filtered and the filtrate acidified with hydrochloric acid. After evaporation, the residue was stirred in methanol, the precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; NH_4OAc / H_2O / CH_3OH 55:0.5:45). The eluent of the desired fraction was evaporated and the residue was stirred in 2-propanone and activated charcoal. The precipitate was filtered off and the filtrate was evaporated. The residue was crystallized first from 2,2'-oxybis-propane and then from acetonitrile. The product was filtered off and dried, yielding 0.3 g (3%) of 11-[1-(ethoxycarbonyl)-4-piperidinylidene]-6,11-dihydro-5H-imidazo[2,1-b]-[3]benzazepine-3-carboxylic acid; mp. 182.2°C (comp. 4.17).

Example 53

To a stirred mixture of 2.93 g of compound (4.03), 1.3 g of sodium acetate and 30 ml of acetic acid was added dropwise a solution of 1.6 g of bromine in 20 ml of acetic acid. After stirring for 1 hour at 30°C, the mixture was evaporated and the residue was taken up in water. The aqueous solution was treated with sodium hydroxide and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5 → CH_2Cl_2 / CH_3OH / CH_3OH:NH_3 90:8:2). The eluent of the desired fraction was evaporated and the residue was boiled in acetonitrile. After cooling, the precipitated product was filtered off and dried, yielding 0.96 g (25.8%) of 2-bromo-6,11-dihydro-3-methyl-11-(1-methyl-4-piperidinylidene)-5H-imidazo-[2,1-b][3]benzazepine; mp. 116.0°C (comp. 4.22).

Example 54

a) A mixture of 6.1 g of 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo-[2,1-b][3]benzazepine-3-carboxaldehyde and 5.3 g of monoethyl ester propanedioic acid in 1 ml of piperidine and 50 ml of pyridine was stirred and refluxed for 4 hours. The

reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane, dried, filtered and evaporated, yielding 13 g (100%) of ethyl 3-[5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepin-3-yl]-2-propenoate (comp. 4.27).

b) A solution of 1.12 g of potassium hydroxide in 40 ml of water was added dropwise to a stirred mixture of 13 g of compound (4.27) in 20 ml of tetrahydrofuran. The mixture was stirred overnight, acidified with HCl and evaporated. The residue was purified by HPLC Lichroprep 18 25µm (eluent : $NH_4OAc/H_2O/CH_3CN$ 0.5/89.5/10 H_2O/CH_3CN 90/10). The eluent of the desired fraction was evaporated and the residue was stirred in 500 ml of 2-propanone, decolourized with activated charcoal and filtered over diatomaceous earth. The filtrate was evaporated and the residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 0.9 g (11.9%) of ethyl (E)-3-[5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b]-[3]benzazepin-3-yl]-2-propenoic acid sesquihydrate; mp. 207.3°C (comp. 4.28).

Example 55

a) A mixture of 2.64 g of 2,5-dimethoxytetrahydrofuran, 3.1 g of compound (1.27), 30 ml of water and 10 ml of acetic acid was stirred for 1.5 hours at 50°C. The mixture was basified with NaOH(aq.) and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile, yielding 1.17 g (33%) of 6,11-dihydro-11-[1-[2-(1H-pyrrol-1-yl)ethyl]-4-piperidinylidene]-5H-imidazo-[2,1-b][3]benzazepine; mp. 165.5°C (comp. 1.55).

b) To 60 ml of N,N-dimethylformamide were added dropwise 5.9 g of phosphoryl chloride. After stirring for 30 minutes at room temperature, there was added a solution of 13.7 g of compound (1.55) in N,N-dimethylformamide and stirring at room temperature was continued for 1 hour. The reaction mixture was poured into a mixture of ice, water and potassium carbonate and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 96:4). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile, yielding 6.4 g (43%) of 1-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-1H-pyrrole-2-carboxaldehyde; mp. 158.5°C (comp. 1.56).

c) To a cooled mixture (ice-bath) of 4.4 g of compound (1.56) and 100 ml of methanol was added portionwise over 15 minutes 1.1 g of sodium tetrahydroborate. After stirring for 1 hour at room temperature, the reaction mixture was evaporated and the residue was

taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 97:3 to 93:7). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile, yielding 2.74 g (62%) of 1-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-ethyl]-1H-pyrrole-2-methanol; mp. 147.4°C (comp. 1.57).

Example 56

a) A mixture of 4.3 g of compound (1.27), 5.2 g of ethyl 2,5-diethoxy-tetrahydofuran-2-carboxylate and 100 ml of acetic acid was stirred for 2 hours at 80°C. The mixture was evaporated and the residue was taken up in water. The whole was basified with potassium carbonate and the product extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 96:4 → 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetontrile, yielding 4.3 g (70%) of ethyl 1-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-1H-pyrrole-2-carboxylate; mp. 158.5°C (comp. 1.58).

b) A mixture of 3.2 g of compound (1.58), 40 ml of sodium hydroxide (1N), 50 ml of tetrahydrofuran and 100 ml of water was stirred for 48 hours at reflux temperature. The reaction mixture was evaporated and the residue was washed with dichloromethane. The whole was neutralized with HCl (1N) and the product was extracted with dichloromethane. The organic layer was dried, filtered and evaporated. The product was crystallized successively from 2-propanone and acetonitrile, yielding 1.06 g (36%) of 1-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-ethyl]-1H-pyrrole-2-carboxylic acid hemihydrate; mp. 166.2°C (comp. 1.59).

Example 57

To a mixture of 3 g of compound (3.23) and 10 ml of tetrahydrofuran was added dropwise a solution of 0.45 g of potassium hydroxide in 20 ml of water. After stirring overnight at room temperature, the reaction mixture was evaporated and the aqueous layer was washed three times with dichloromethane. The aqueous layer was discoloured with activated charcoal, filtered over diatomaceous earth and concentrated. The aqueous layer was neutralized with HCl till pH=7. The precipitate was filtered off, washed with water and dried, yielding 1.26 g (40%) of 4-(8-fluoro-5,6-dihydro-11H-imidazo[2,1-b]-[3]benzazepin-11-ylidene)-1-piperidinepropanoic acid dihydrate; mp. 136.1°C (comp. 3.31).

Example 58

A mixture of 1.9 g of compound (3.28) and 50 ml of hydrobromic acid 48% (aq.) was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water and basified with potassium carbonate. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 94:6 → 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate salt (2:3) in 2-propanol; yielding 1.15 g (42%) of 4-[2-[4-(5,6-dihydro-8-methyl-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-ethyl]phenol hemiethanolate hemihydrate (E)-2-butenedioate (2:3); mp. 176.0°C (comp. 3.30).

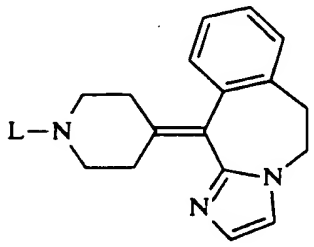
Example 59

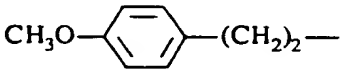
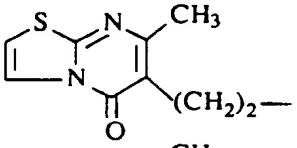
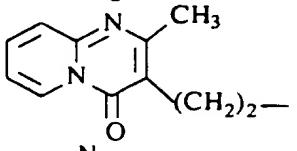
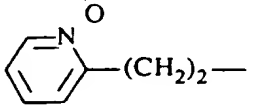
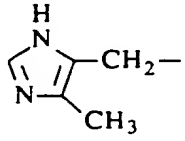
a) A mixture of 4.3 g of compound (4.16), 9 g of methyl (methylthio)methanesulfoxide 97%, 50 ml of tetrahydrofuran and 20 ml of a solution of benzyltrimethylammonium hydroxide in methanol 40% was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was co-evaporated with methylbenzene (2x) and then taken up in 50 ml of methanol. This solution was cooled on ice and gasueous hydrochloride was bubbled through for 1/2 hour. After stirring overnight, the whole was evaporated. The residue was taken up in water and basified with potassium carbonate. The product was extracted with dichloromethane and further purified by column chromatography (silica gel ; CH_2Cl_2 / $C_2H_5OH(NH_3)$ 97:3). The desired fraction was evaporated, yielding 3.15 g (29.9%) of methyl [5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo-[2,1-b][3]benzazepin-3-yl]acetate (comp. 4.30).

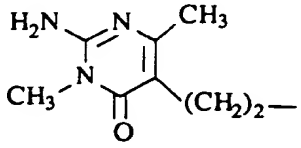
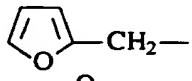
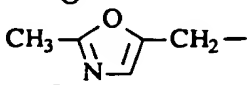
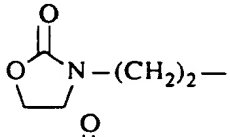
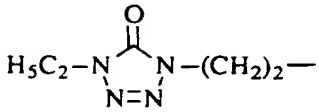
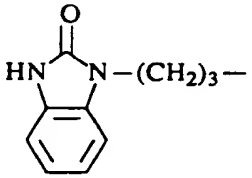
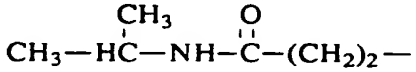
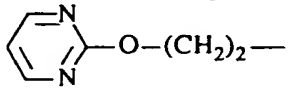
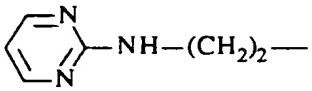
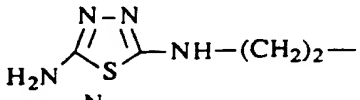
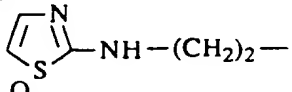
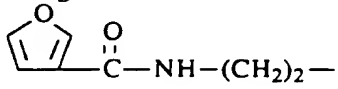
b) To a stirred mixture of 3.15 g of compound (4.30) and 10 ml of tetrahydrofuran there was added dropwise a solution of 0.56 g of potassium hydroxide in 20 ml of water. Stirring was continued overnight. The organic solvent was evaporated and the remaining aqueous layer was successively washed with dichloromethane (3x) and stirred with activated charcoal. After filtration, the whole was concentrated and then neutralized to pH 7. The product was filtered off and purified by column chromatography (RP 18 ; CH_3COONH_4 (0.5% in H_2O) / CH_3CN 90:10). The eluent of the desired fraction was evaporated and the residue was recrystallized from acetonitrile, yielding 1.39 g (45.9%) of [5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepin-3-yl]acetic acid (comp. 4.31).

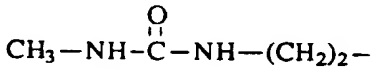
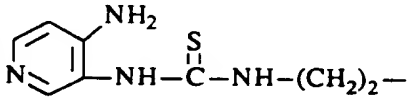
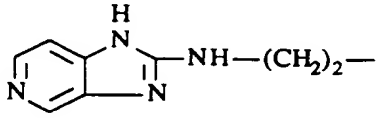
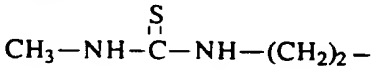
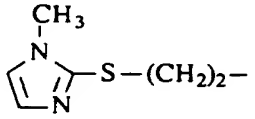
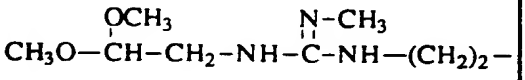
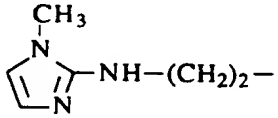
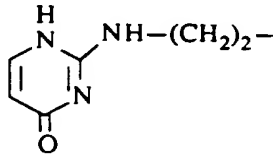
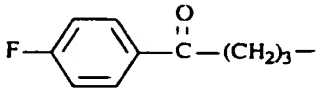
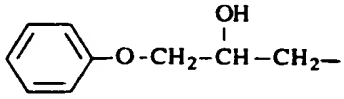
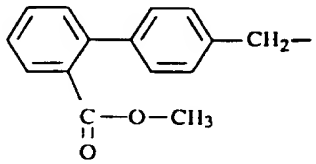
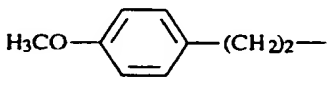
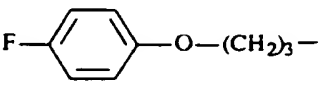
All compounds listed in Tables 1-7 were prepared following methods of preparation described in examples 13-59, as is indicated in the column Ex. No.

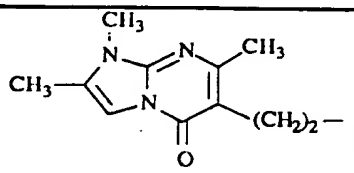
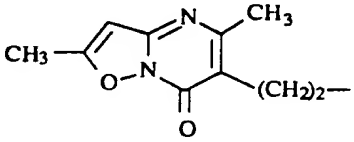
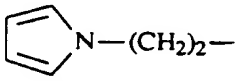
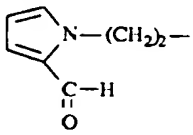
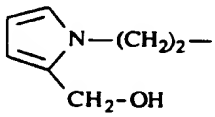
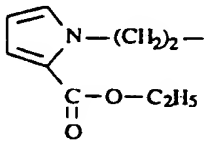
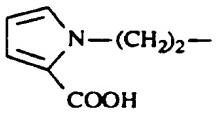
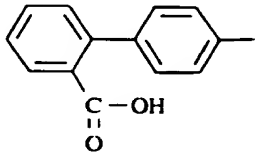
Table 1



Co. No.	Ex. No.	L-	Physical data
1.01	13	CH_3-	mp. 209.3°C / CF_3SO_3H
1.02	13	CH_3-	mp. 154.5°C
1.03	19	H_5C_2OOC-	mp. 170.6°C
1.04	21	H-	mp. 192.5°C / 1/2 H_2O . 2(E)*
1.05	34	C_2H_5-	mp. 184.2°C / 2(Z)*
1.06	35	$CH_3CH(CH_3)$-	mp. 183.6°C / 2(Z)*
1.07	32	CH_2=CH-CH_2-	mp. 160.8°C / 2(Z)*
1.08	28	CH_2=C(CH_3)-CH_2-	mp. 179.5°C / 3/2(E)*
1.09	29	CH_3-C(CH_3)=CH-CH_2-	mp. 127.2°C
1.10	25	C_6H_5-CH=CH-CH_2-	mp. 172.2°C / (E)
1.11	33	C_6H_5-CH_2-	mp. 207.2°C
1.12	26		mp. 180.5°C / 2$(COOH)_2$
1.13	26		mp. 181.8°C
1.14	25		mp. 197.8°C / H_2O . 3(E)*
1.15	37		mp. 163.8°C
1.16	28		mp. 199.0°C

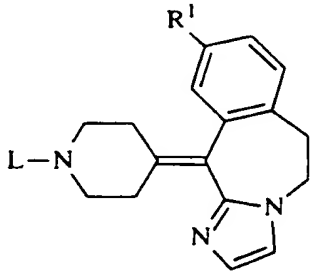
Co. No.	Ex. No.	L-	Physical data
1.17	25		mp. 257.4°C
1.18	34		mp. 160.3°C
1.19	26		mp. 162.1°C / H_2O . 2(E)*
1.20	25		mp. 188.8°C / 3/2(E)*
1.21	25		mp. 170.7°C / 2(Z)*
1.22	25		mp. 194.7°C
1.23	25	C_2H_5-O-$(CH_2)_2$-	mp. 176.5°C / 2(Z)*
1.24	25		mp. 165.5°C
1.25	25	H_5C_2OOC-NH-$(CH_2)_2$-	mp. 167.2°C / 2(E)*
1.26	27	NC-CH_2-	mp. 220.4°C
1.27	21	H_2N-$(CH_2)_2$-	-
1.28	39	H_2N-$(CH_2)_2$-	mp. 186.6°C / 1/2 H_2O . 3(E)*
1.29	38	HO-$(CH_2)_2$-	mp. 225.1°C / CF_3SO_3H
1.30	38	HO-$(CH_2)_2$-	mp. 145.7°C / 2(Z)*
1.31	41		mp. 172.6°C / 2(Z)*
1.32	42		mp. 165.1°C
1.33	43		mp. 251.4°C
1.34	43		mp. 205.5°C / 1/2H_2O / 4**
1.35	44		mp. 202.9°C / 2(Z)*

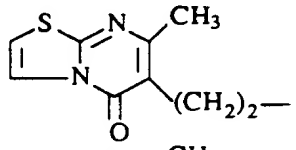
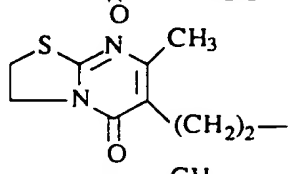
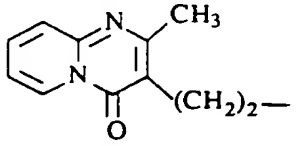
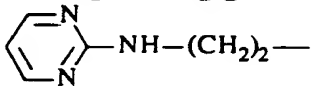
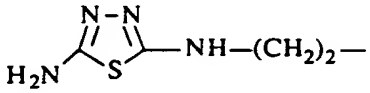
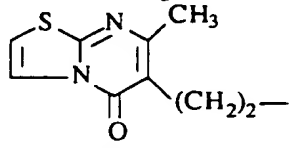
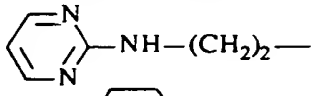
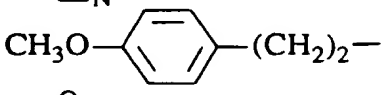
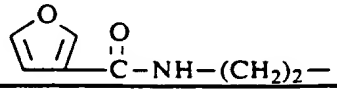
Co. No.	Ex. No.	L-	Physical data
1.36	45		mp. 178.1°C
1.37	46a	$SCN\text{-}(CH_2)_2\text{-}$	
1.38	46b		-
1.39	46c		mp. 203.0°C / 1/2H_2O . 3(E)*
1.40	47		mp. 155.2°C / 1/2H_2O
1.41	48	$Cl\text{-}(CH_2)_2\text{-}$	mp. 169.9°C / 2(Z)*
1.42	48		mp. 265.4°C (dec.) / 2**
1.43	49a		HI
1.44	49b		mp. 153.9°C / 2H_2O . 3**
1.45	50		mp. 234.8°C / 2H_2O . 3HCl
1.46	26		mp. 161.0°C
1.47	38		2-(E)* / mp. 156.4°C
1.48	28	$H_5C_2\text{-}O\text{-}CO\text{-}(CH_2)_2\text{-}$	-
1.49	27		mp. 131.5°C
1.50	27		(E)* . 1/2 H_2O . 1/2 ethanolate / mp. 127.4°C
1.51	25		mp. 130.3°C

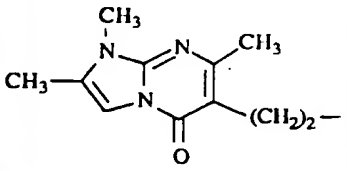
Co. No.	Ex. No.	L-	Physical data
1.52	25		mp. 195.9°C
1.53	25		mp. 202.9°C
1.54	24	CH_3-CO	mp. 182.1°C
1.55	55a		mp. 165.5°C
1.56	55b		mp. 158.5°C
1.57	55c		mp. 147.4°C
1.58	56a		mp. 158.5°C
1.59	56b		1/2 H_2O / mp. 166.2°C
1.60	57	HOOC-$(CH_2)_2$-	2 H_2O / mp. 154.9°C
1.61	57		ethanolate(1:1) / mp. 208.6°C

* : 2-butenedioate ** : cyclohexanesulfamate

Table 2

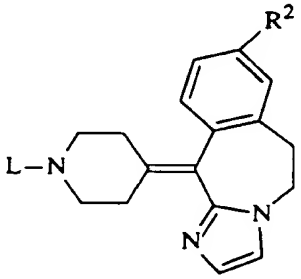


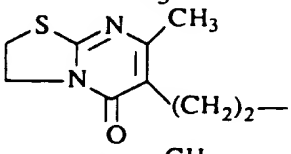
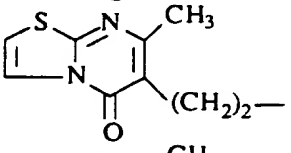
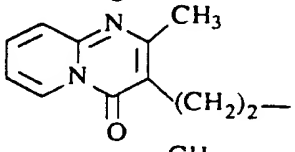
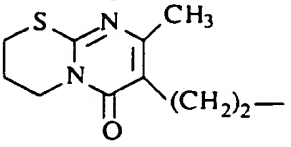
Co. No.	Ex. No.	L-	R^1	Physical data
2.01	13	CH_3-	F	mp. 195.7°C / 2(E)*
2.02	19	H_5C_2OOC-	F	mp. 175.2°C
2.03	21	H-	F	mp. 180.1°C
2.04	31	CH_3-C(CH_3)=CH-CH_2-	F	mp. 203.4°C / 2(Z)*
2.05	25		F	mp. 168.9°C / 3/2 H_2O . 5/2(E)*
2.06	25		F	mp. 162.2°C / 3/2 H_2O . 5/2(E)*
2.07	25		F	mp. 201.9°C / 3(E)*
2.08	30	NC-CH_2-	F	mp. 198.3°C
2.09	39	H_2N-(CH_2)$_2$-	F	-
2.10	42		F	mp. 165.1°C / 3(Z)*
2.11	43		F	mp. 238.6°C
2.12	13	H-	CH_3-	mp. 203.1°C
2.13	24	H_5C_2OOC-	CH_3-	mp. 156.5°C
2.14	33	CH_3-	CH_3-	mp. 214.3°C
2.15	26		CH_3-	mp. 202.2°C
2.16	30	NC-CH_2-	CH_3-	-
2.17	39	H_2N-(CH_2)$_2$-	CH_3-	mp. 219.3°C / 3(E)*
2.18	42		CH_3-	mp. 131.1°C
2.19	26		CH_3-	mp. 192.6°C / 5/2($COOH)_2$
2.20	44		CH_3-	mp. 214.2°C / 2(Z)*

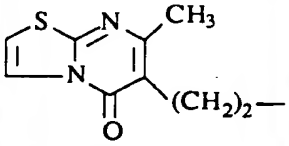
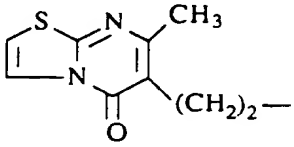
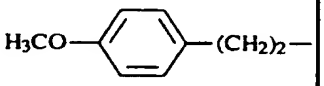
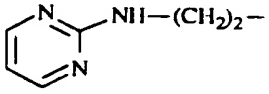
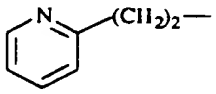
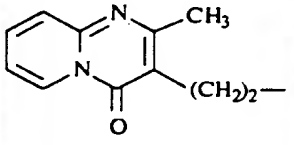
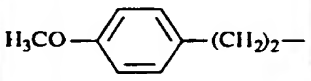
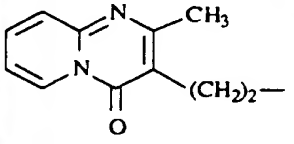
Co. No.	Ex. No.	L-	R^1	Physical data
2.21	13	CH_3-	Br	mp. 213.4°C
2.22	25		F	mp. 187.2°C / H_2O

* : 2-butenedioate

Table 3



Co. No.	Ex. No.	L-	R^2	Physical data
3.01	14	CH_3-	CH_3O-	mp. 190.3°C / 2(Z)*
3.02	19	H_5C_2OOC-	CH_3O-	mp. 104.4°C
3.03	21	H-	CH_3O-	mp. 184.4°C
3.04	13	H-	CH_3-	mp. 221.9°C / 2(E)*
3.05	33	CH_3-	CH_3-	mp. 211.0°C / 2(E)*
3.06	25		CH_3-	mp. 199.8°C
3.07	25		CH_3-	mp. 214.2°C
3.08	25		CH_3-	mp. 162.3°C / H_2O . 3(E)*
3.09	25		CH_3-	mp. 235.1°C / $2H_2O$. 3HCl
3.10	13	CH_3-	Cl	mp. 186.6°C
3.11	19	H_5C_2OOC-	Cl	mp. 140.3°C

Co. No.	Ex. No.	L-	R^2	Physical data
3.12	23	H-	Cl	mp. 197.1°C
3.13	26		Cl	mp. 217.6°C
3.14	30	$NC-CH_2-$	Cl	-
3.15	15	CH_3-	F	mp. 152.4°C
3.16	19	H_5C_2OOC-	F	mp. 149.4°C
3.17	21	H-	F	-
3.18	26		F	mp. 192.2°C / H_2O . 3/2(E)*
3.19	29		OCH_3	3/2(E)* . ethanolate / mp. 150.3°C
3.20	32		Cl	ethanedioate(1:2) / mp. 206.7°C
3.21	37		Cl	mp. 171.3°C
3.22	39	$H_2N-(CH_2)_2-$	Cl	-
3.23	28	$H_5C_2-O-CO-(CH_2)_2-$	F	mp. 114.6°C
3.24	27	$NC-CH_2-$	F	mp. 204.7°C
3.25	27		F	mp. 211.6°C
3.26	27		F	mp. 149.1°C
3.27	25		Cl	ethanedioate(2:5) , 1/2 ethanolate / mp. 170.7°C

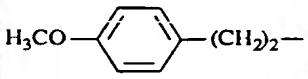
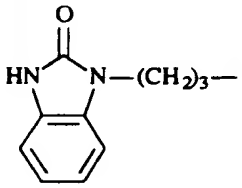
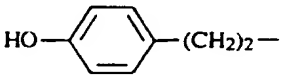
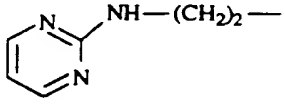
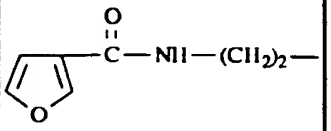
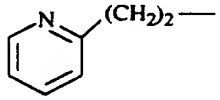
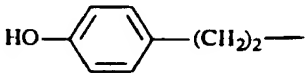
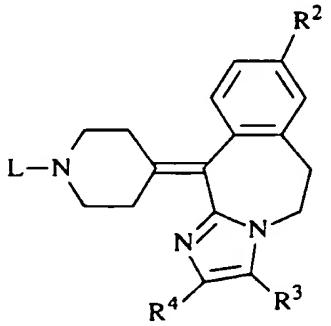
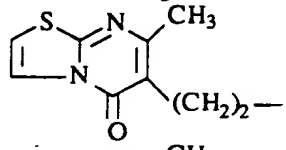
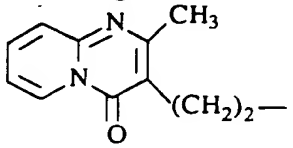
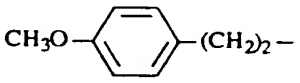
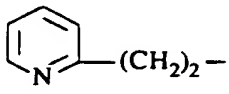
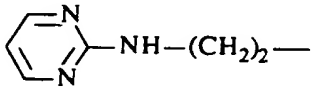
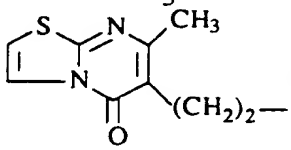
Co. No.	Ex. No.	L-	R^2	Physical data
3.28	25		CH_3	cyclohexylsulfamate(1:2) , H_2O / mp. 149.8°C
3.29	25		CH_3	(E)-2-butenedioate(1:2) , 1/2 H_2O / mp. 200.3°C
3.30	58		CH_3	(E)-2-butenedioate(2:3) . 1/2 ethanolate . 1/2 H_2O / mp. 176.0°C
3.31	57	$HOOC-(CH_2)_2-$	F	2 H_2O / mp. 136.1°C
3.32	42		F	mp. 191.2°C
3.33	44		F	mp. 173.5°C
3.34	37		F	mp. 177.2°C
3.35	58		F	-
3.36	39	$H_2N-(CH_2)_2-$	F	mp. 141.5°C

Table 4

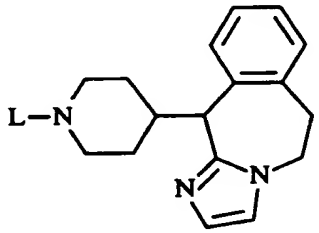


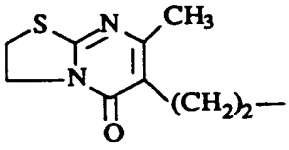
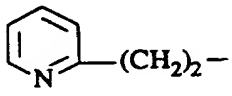
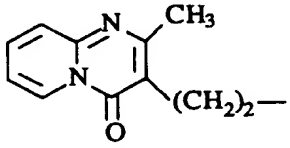
Co. No.	Ex. No.	L-	R^2	R^3	R^4	Physical data
4.01	17	CH_3-	H	H	C_6H_5	mp. 171.5 °C
4.02	13	H	H	-CH_3	H	mp. 167.0 °C
4.03	33	CH_3-	H	-CH_3	H	mp. 172.2 °C
4.04	25		H	-CH_3	H	mp. 212.4 °C
4.05	25		H	-CH_3	H	mp. 186.3 °C / 3 (E)* . H_2O
4.06	25		H	-CH_3	H	mp.150.6 °C / 5/2$(COOH)_2$. H_2O
4.07	37		H	-CH_3	H	mp.180.2 °C / 7/2$(COOH)_2$
4.08	30	NC-CH_2-	H	-CH_3	H	mp. 226.5 °C
4.09	39	H_2N-$(CH_2)_2$-	H	-CH_3	H	-
4.10	42		H	-CH_3	H	mp. 171.3 °C
4.11	20	C_2H_5OOC-	H	-CH_2OH	H	mp. 191.9 °C
4.12	21	H	H	-CH_2OH	H	mp.>200 °C dec./ 5/2 (E)*
4.13	33	CH_3-	H	-CH_2OH	H	mp. 228.3 °C
4.14	26		H	-CH_2OH	H	-
4.15	51	C_2H_5OOC-	H	-CHO	H	mp. 138.2 °C
4.16	51	CH_3-	H	-CHO	H	mp. 171.6 °C
4.17	52	C_2H_5OOC-	H	-COOH	H	mp. 182.2 °C
4.18	20	C_2H_5OOC-	H	-CH_2OH	-CH_2OH	-
4.19	21	H-	H	-CH_2OH	-CH_2OH	-
4.20	33	CH_3-	H	-CH_2OH	-CH_2OH	mp. 206.3 °C
4.21	36	CH_3-	H	-CH_3	-CH_2OH	mp. 166.8 °C
4.22	53	CH_3-	H	-CH_3	-Br	mp.116.0°C

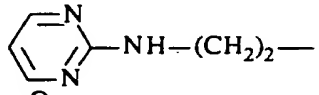
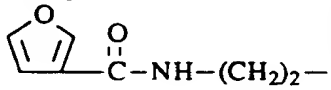
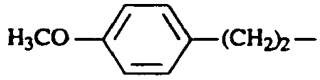
Co. No.	Ex. No.	L-	R^2	R^3	R^4	Physical data
4.23	52	CH_3-	H	-COOH	H	mp. 241.3°C
4.24	51	CH_3-	F	-CHO	H	mp. 176.5°C
4.25	36	CH_3-	F	$-CH_2OH$	H	mp. 181.5°C
4.26	36	CH_3-	F	$-CH_2OH$	$-CH_2OH$	mp. 220.0°C
4.27	54a	CH_3-	H	$-CH=CH-COOC_2H_5$	H	-
4.28	54b	CH_3-	H	-CH=CH-COOH	H	(E) / $3/2H_2O$ mp. 207.3°C
4.29	52	CH_3-	F	-COOH	H	1/2 H_2O mp. 261.6°C
4.30	59a	CH_3-	H	$-CH_2-COOCH_3$	H	-
4.31	59b	CH_3-	H	$-CH_2$-COOH	H	-

* = 2-butenedioate

Table 5

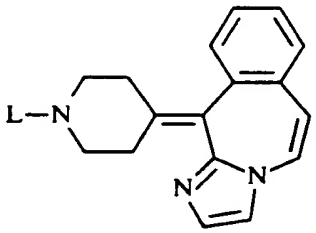


Co. No.	Ex. No.	L-	Physical data
5.01	16	H-	mp. 220.2 °C / 2 (E)*
5.02	34	CH_3-	mp. 117.8 °C / 1/2 H_2O
5.03	25		mp. 221.6 °C / 2 $(COOH)_2$ / 1/2 H_2O
5.04	37		mp. 170.3 °C
5.05	25		mp. 193.3 °C
5.06	27	NC-CH_2-	mp. 194.7 °C / 1/2 (E)*

Co. No.	Ex. No.	L-	Physical data
5.07	40	$H_2N-CH_2-CH_2-$	-
5.08	42		mp. 175.1 °C / 7/2 (E)*
5.09	44		mp. 203.5 °C
5.10	25		cyclohexylsulfamate(1:2) 1/2 H_2O / mp. 125.4°C
5.11	24	CH_3-CO-	mp. 153.8°C

* = 2-butenedioate

Table 6



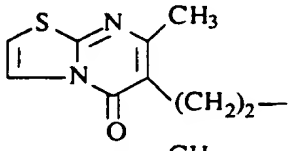
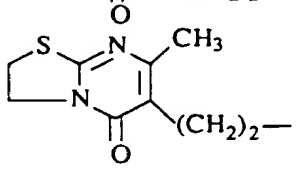
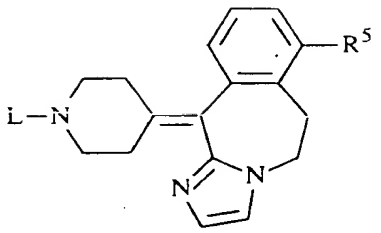
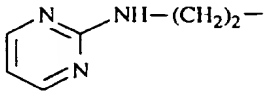
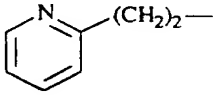
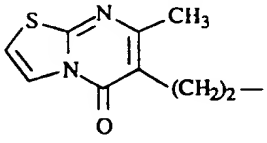
Co. No.	Ex. No.	L-	Physical data
6.01	18	CH_3-	mp. 135.8 °C
6.02	19	C_2H_5OOC-	-
6.03	22	H-	mp. 246.9 °C / 2HBr 1/2 H_2O
6.04	27		mp.206.4 °C / 2$(COOH)_2$ 1/2 H_2O
6.05	26		mp.158.9 °C / 5/2$(COOH)_2$ .1/2 H_2O

Table 7



Co. No.	Ex. No.	R^5	L-	Physical data
7.01	15	-Cl	CH_3-	mp. 181.9 °C
7.02	33	-CH_3	CH_3-	mp. 184.2°C
7.03	42	-CH_3		ethanedioate (2:7) 1/2 H_2O /mp. 171.2°C
7.04	37	-CH_3		(E)-2-butenedioate(2:3) 1/2 H_2O /162.2°C
7.05	39	-CH_3	H_2N-$(CH_2)_2$-	(Z)-2-butenedioate(1:3) / mp. 192.0°C
7.06	13	-CH_3	H	-
7.07	13	-CH_3	H	2 HCl
7.08	13	-F	CH_3-	mp. 164.6°C
7.09	27	-CH_3	NC-CH_2-	mp. 194.1°C
7.10	25	-CH_3		mp. 224.3°C

C. Composition Examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a compound of formula (VII) wherein Q represents (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino, a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 60 : Oral drops

500 g of the A.I. is dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the

polyethylene glycol at 60~80°C. After cooling to 30~40°C there are added 35 l of polyethylene glycol and the mixture is stirred well. Then there is added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there are added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of the A.I. The resulting solution is filled into suitable containers.

Example 61 : Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example 62 : Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I..

Example 63 : Film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinyl-pyrrolidone (Kollidon-K 90®) in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose (Avicel®) and 15 g hydrogenated vegetable oil (Sterotex ®). The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG®) in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of

dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109®) and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Example 64 : Injectable solutions

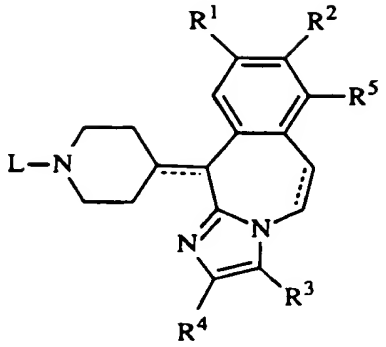
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate are dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there are added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I..The solution is cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg A.I. per ml. The solution is sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 65 : Suppositories

3 g A.I. is dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g surfactant (SPAN®) and triglycerides (Witepsol 555®) q.s. ad 300 g are molten together. The latter mixture is mixed well with the former solution. The thus obtained mixture is poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg of the A.I.

Claims

1. A compound having the formula



(I),

a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein each of the dotted lines independently represents an optional bond,

R^1 represents hydrogen, halo, C_{1-4}alkyl, or C_{1-4}alkyloxy;

R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen, C_{1-4}alkyl or halo;

L represents hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one substituent selected from the group consisting of hydroxy, halo, C_{1-4}alkyloxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy, hydroxycarbonyl-C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl, aryloxy and arylcarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl;

wherein each aryl is phenyl or phenyl substituted with halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, aminocarbonyl or phenyl substituted with C_{1-4}alkyloxycarbonyl or hydroxycarbonyl; or,

L represents a radical of formula

-Alk-Y-Het^1 (a-1),

-Alk-NH-CO-Het^2 (a-2) or

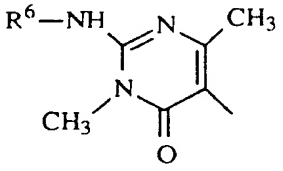
-Alk-Het^3 (a-3); wherein

Alk represents C_{1-4}alkanediyl;

Y represents O, S or NH;

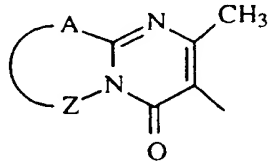
Het^1, Het^2 and Het^3 each represent furanyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4}alkyl substituents; pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxyC_{1-4}alkyl, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl or one or two C_{1-4}alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4}alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4}alkyl, C_{1-4}alkyloxy, amino, hydroxy or halo; imidazo[4,5-c]pyridin-2-yl; and

Het^3 may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C_{1-4}alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



(b-1)

or



(b-2)

wherein

R^6 represents hydrogen or C_{1-4}alkyl; and

A-Z represents -S-CH=CH-, -S-CH_2-CH_2-, -S-CH_2-CH_2-CH_2-, -CH=CH-CH=CH-, -CH_2-CH_2-CH_2-CH_2-, -N(CH_3)-C(CH_3)=CH- or -CH=C(CH_3)-O-;

provided that 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine is ecxluded.

2. A compound according to claim 1 wherein L is C_{1-4}alkyl or C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl.

3. A compound according to claim 1 wherein

R^3 represents hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-4}alkyl or hydroxycarbonyl;

R^4 represents hydrogen, halo or hydroxyC_{1-4}alkyl; and

L represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylaminoC_{1-4}alkyl, aryl-C_{1-4}alkyl, propenyl, or

L is a radical of formula (a-1), (a-2) or (a-3), wherein

Het^1, Het^2, and Het^3 each represent furanyl, oxazolyl or thiazolyl each optionally substituted with C_{1-4}alkyl; thiadiazolyl optionally substituted with amino, pyridinyl; or pyrimidinyl each optionally substituted with hydroxy; imidazo[4,5-c]pyridin-2-yl; and

Het^3 may also represent a radical of formula (b-2).

4. A compound according to claim 3 wherein

R^1 represents hydrogen or halo;

R^2 represents hydrogen, halo or C_{1-4}alkyloxy; and

L represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, or a radical of formula (a-1), wherein Y represents NH.

5. A compound according to claim 1 wherein said compound is selected from the group consisting of

5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine;

9-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine;

11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-methanol;

8-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-carboxaldehyde;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-carboxylic acid;

7-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine; and

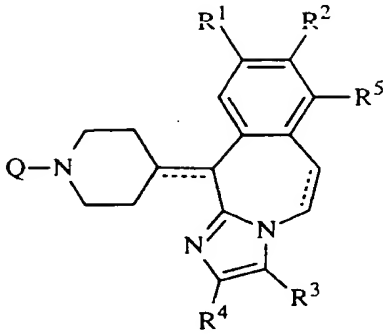
4-(8-fluoro-5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine-propanoic acid dihydrate.

6. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

7. A method of preparing a pharmaceutical composition as claimed in claim 6, characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5 is intimately mixed with a pharmaceutical carrier.

8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

9. A compound having the formula



(VII),

an acid addition salt thereof or a stereochemically isomeric form thereof, wherein each of the dotted lines independently represents an optional bond,

R^1 represents hydrogen, halo, C_{1-4}alkyl, or C_{1-4}alkyloxy;

R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

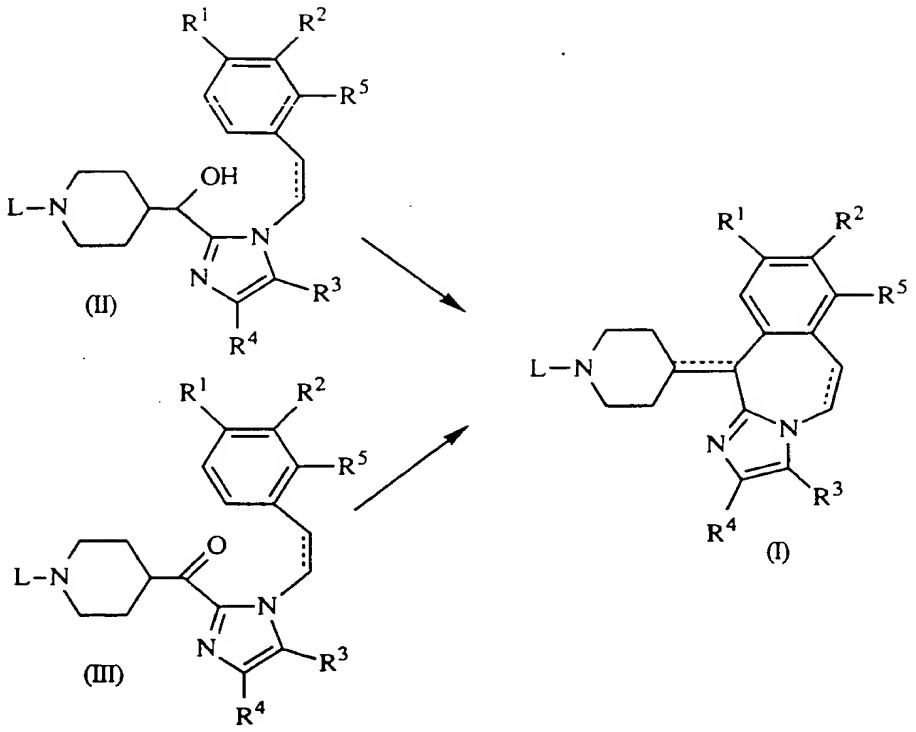
R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen, C_{1-4}alkyl or halo;

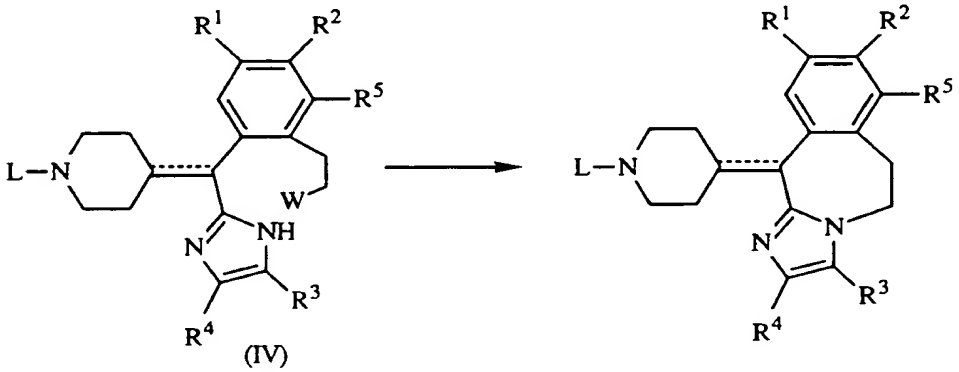
Q represents (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with halo, cyano, amino, isothiocyanato, (4-amino-3-pyridinyl)-aminothiocarbonylamino, $(CH_3O)_2CH\text{-}CH_2\text{-}NH\text{-}C(=NCH_3)\text{-}NH$- or methylsulfonyloxy; provided that 1-acetyl-4-(5,6-dihydro-11H-imidazol[1,2-b][3]-benzazepine-11-ylidene)piperidine is excluded.

10. A process for preparing a compound as defined in any one of claims 1 to 5, characterized by

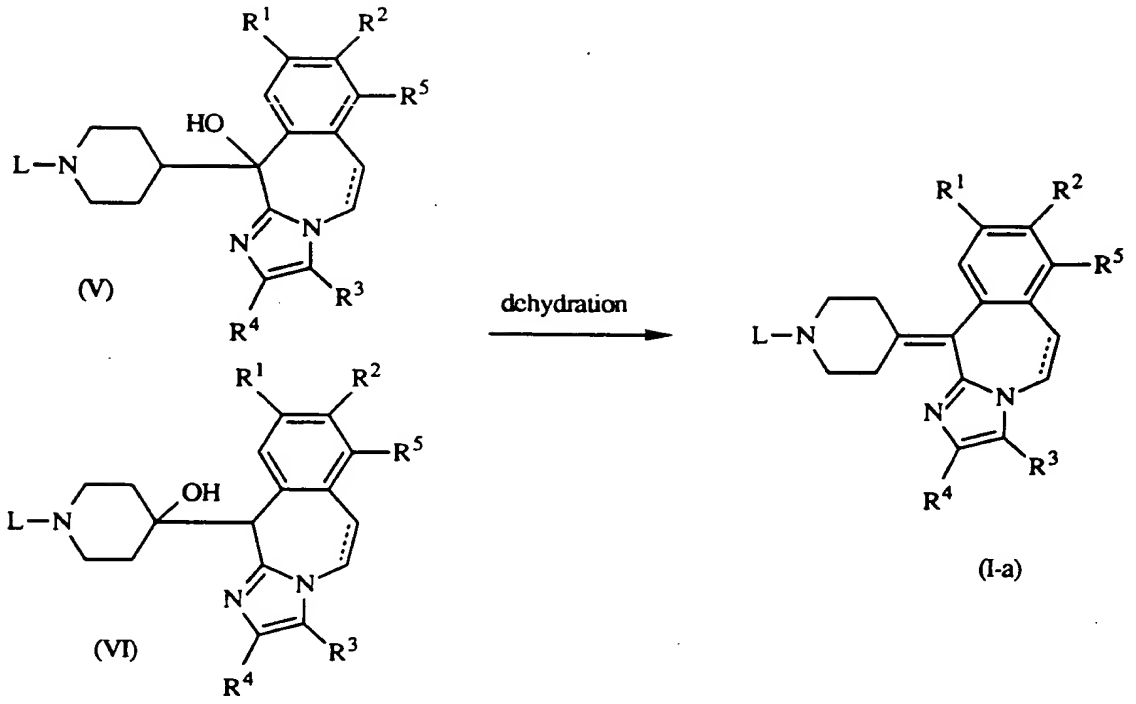
a) cyclizing an alcohol of formula (II) or a ketone of formula (III) in the presence of an acid;



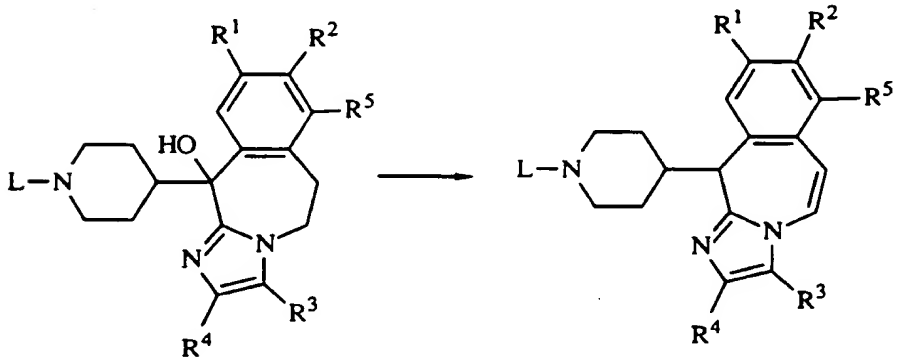
b) cyclizing an intermediate of formula (IV) wherein W represents a reactive leaving group, thus yielding a compound of formula (I) wherein the central ring of the tricyclic moiety does not contain an optional bond;



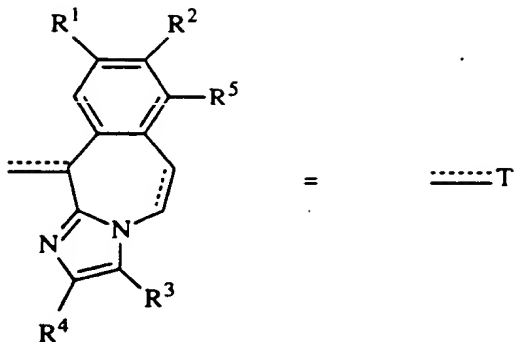
c) dehydrating an alcohol of formula (V) or (VI) in the presence of a dehydrating reagent, thus yielding a compound of formula (I) wherein a double bond exists between the piperidinyl and the tricyclic moiety;



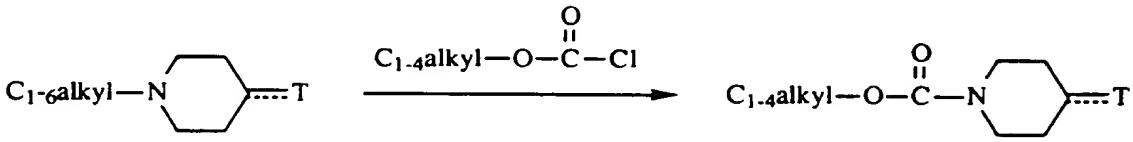
d) dehydrating an alcohol of formula (V) wherein the central ring of the tricyclic moiety does not contain an optional bond, in the presence of a dehydrating reagent, thus yielding a compound of formula (I) with a double bond in the tricyclic moiety and a single bond bridging the tricyclic moiety and the piperidine;



e) reacting an intermediate of formula (I-b) wherein ⁼⁼T represents an imidazo[2,1-b]-[3]benzazepine moiety of formula

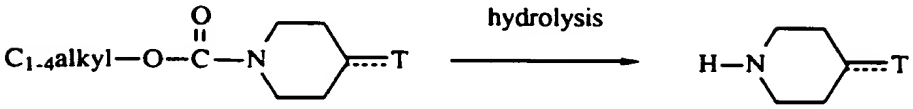


with C_{1-4}alkylchloroformate in the presence of a base and in a reaction-inert solvent yielding a compound of formula (VII-a)



(I-b) (VII-a)

which can be hydrolyzed to a compound of formula (I-c)

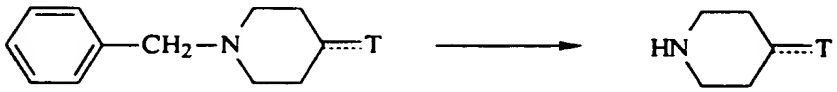


(VII-a) (I-c)

in the presence of an acid or a base;

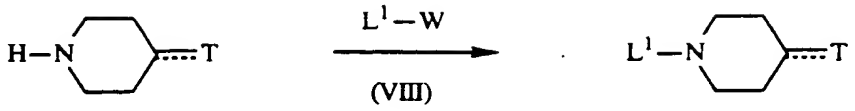
f) reacting a compound of formula (I-b) with an α-halo-C_{1-4}alkyl chloroformate in a reaction-inert solvent yielding a compound of formula (I-c);

g) debenzylating a compound of formula (I-d) by catalytic hydrogenation in the presence of hydrogen and a catalyst in a reaction-inert solvent;



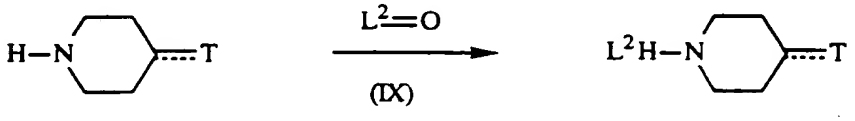
(I-d) (I-c)

h) N-alkylating a compound of formula (I-c) with a reagent of formula (VIII) in a reaction-inert solvent, optionally in the presence of a base;



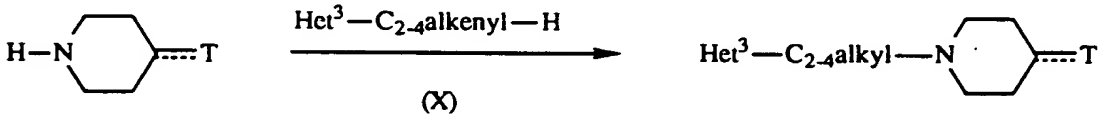
(I-c) (I-e)

i) reductively N-alkylating a compound of formula (I-c) with a reagent of formula $L^2=O$ (IX) wherein L^2 represents a geminal bivalent C_{1-6}alkylidene radical which optionally may be substituted, in a reaction-inert solvent, in the presence of a base;



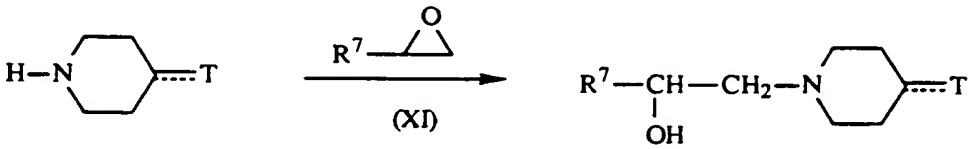
(I-c) (I-f)

j) reacting a compound of formula (I-c) with a reagent of formula (X) in a reaction-inert solvent;



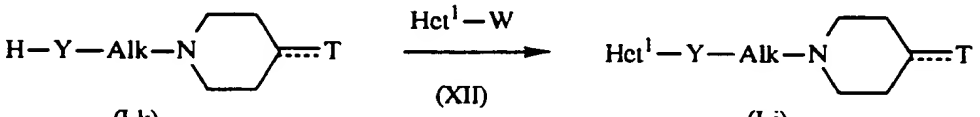
(I-c) (I-g)

k) reacting a compound of formula (I-c) with an epoxide of formula (XI) wherein R^7 represents hydrogen, C_{1-4}alkyl or aryloxyC_{1-4}alkyl in a reaction-inert solvent;



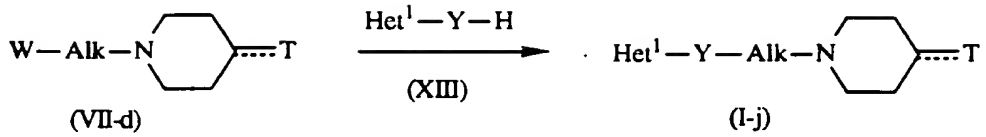
(I-c) (I-h)

l) reacting a compound of formula (I-k) with a reagent of formula (XII) in a reaction-inert solvent in the presence of a base;



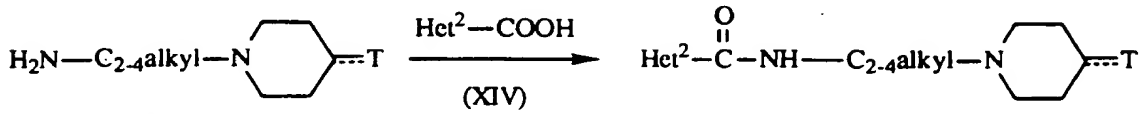
(I-k) (I-j)

m) reacting a compound of formula (VII-d) with a reagent of formula (XIII) in a reaction-inert solvent in the presence of a base;



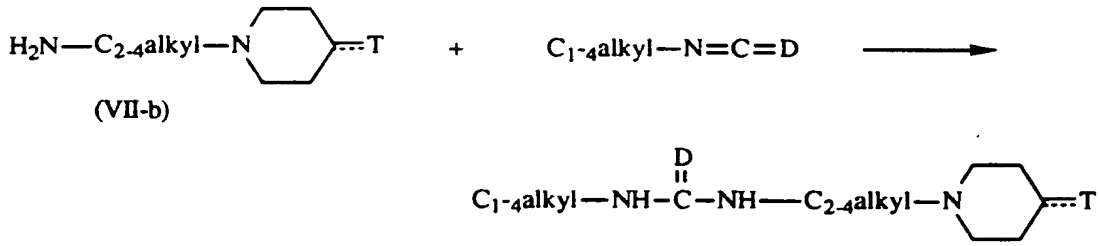
(VII-d) (I-j)

n) N-acylating a compound of formula (VII-b) with a carboxylic acid of formula (XIV) in a reaction-inert solvent;



(VII-b) (I-l)

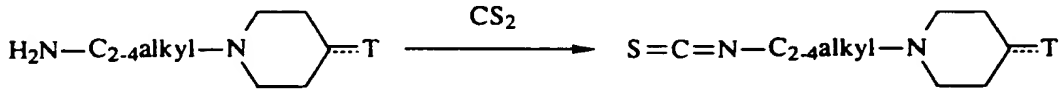
o) reacting a compound of formula (VII-b) with a C_{1-4}alkyliso(thio)cyanate in a reaction-inert solvent;



(VII-b)

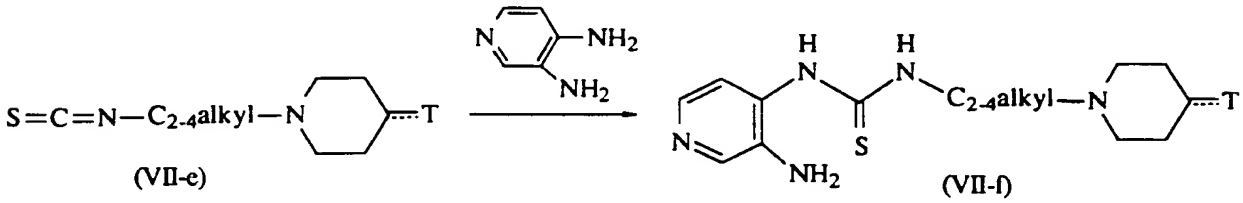
D = S : (I-m-1)
D = O : (I-m-2)

p) reacting a compound of formula (VII-b) with carbon disulfide in the presence of a dehydrating reagent yielding a compound of formula (VII-e)



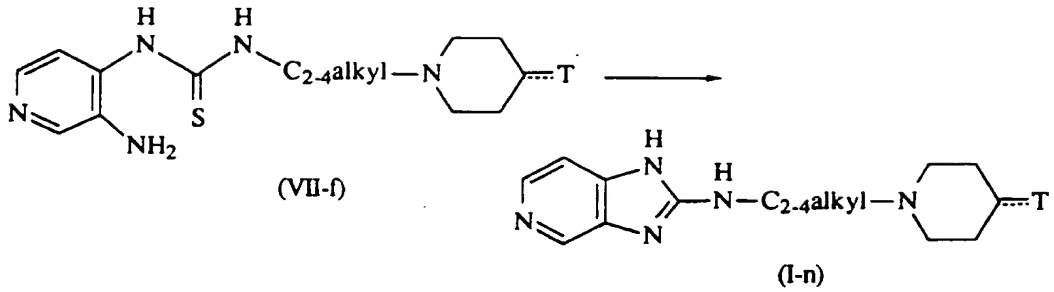
(VII-b) (VII-e)

which can be reacted with 3,4-diaminopyridine in a reaction-inert solvent, thus yielding a compound of formula (VII-f)



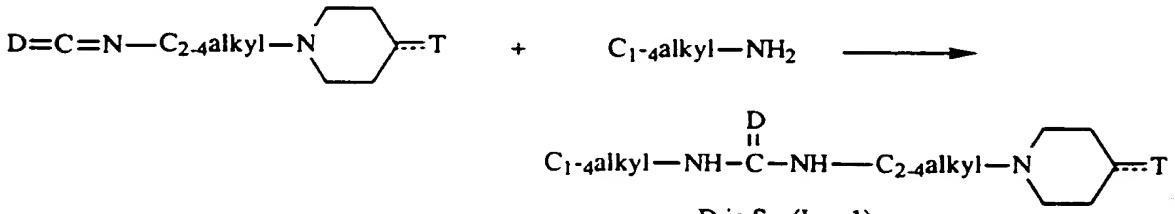
(VII-e) (VII-f)

which can be cyclized with a metal oxide into a compound of formula (I-n);



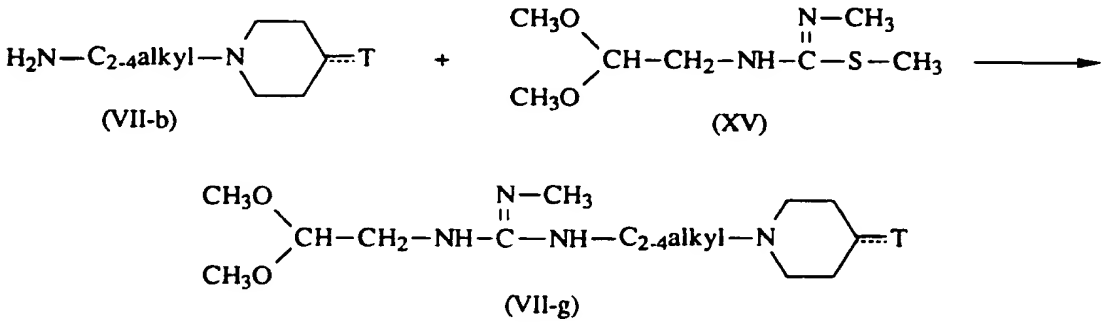
(VII-f) (I-n)

q) reacting a compound of formula (VII-e) or the corresponding isocyanate with C_{1-4}alkylamine in a reaction-inert solvent;



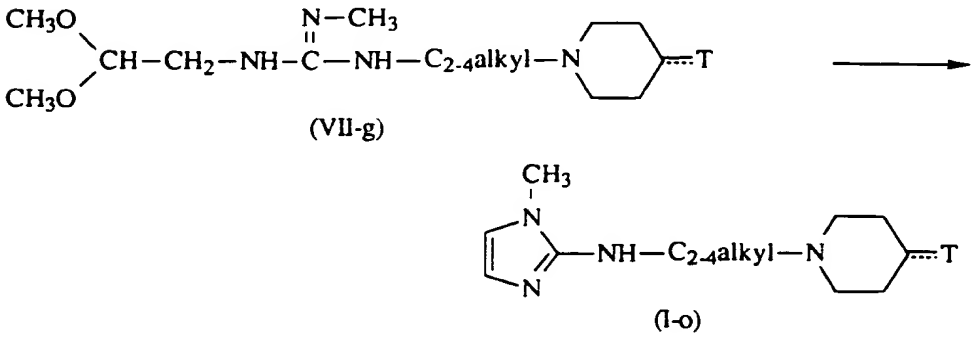
D is S : (I-m-1)
D is O : (I-m-2)

r) reacting a compound of formula (VII-b) with a reagent of formula (XV) in a reaction-inert solvent yielding a compound of formula (VII-g)



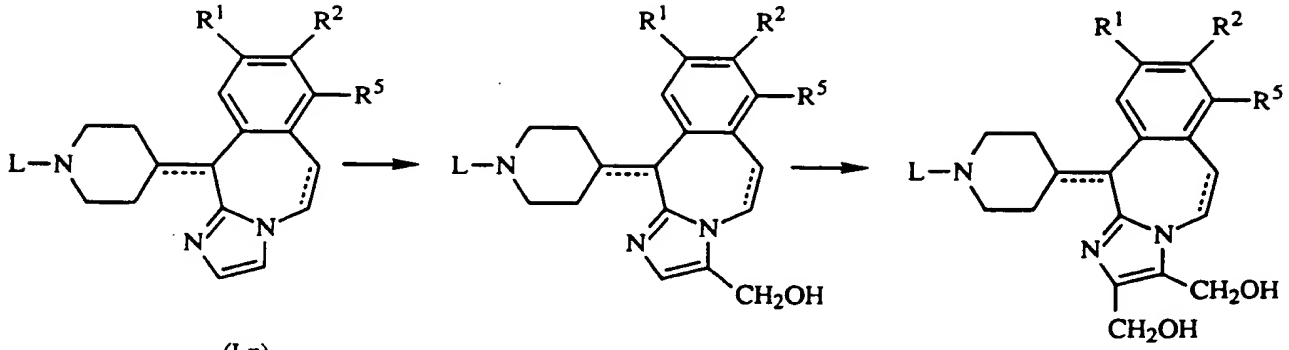
(VII-b) (XV) (VII-g)

which can be cyclized in an acidic aqueous solution into a compound of formula (I-o);



(VII-g) (I-o)

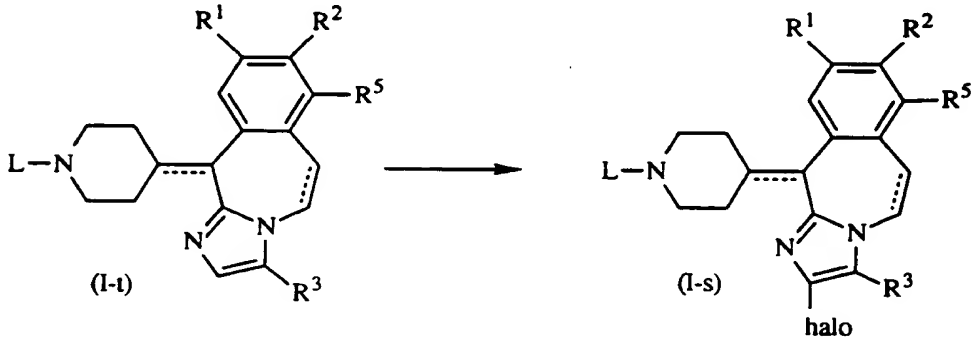
s) reacting a compound of formula (I-p) with formaldehyde optionally in the presence of a carboxylic acid-carboxylate mixture



(I-p) (I-q) (I-r)

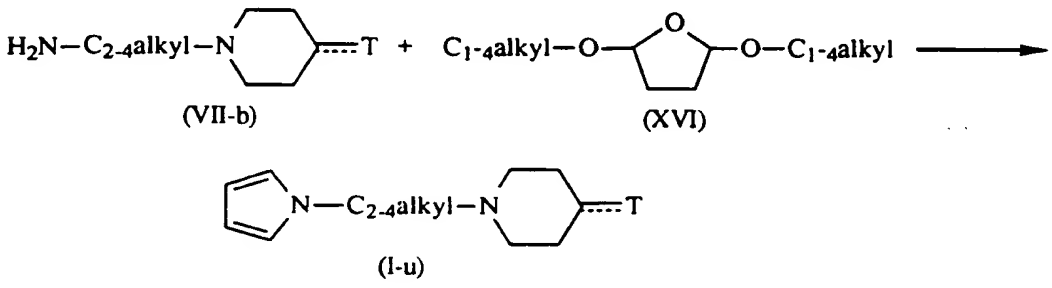
and optionally further oxidizing the compound (I-q) and (I-r) to the corresponding aldehyde or carboxylic acid;

t) halogenating a compound of formula (I-t) in the presence of a halogenating reagent;



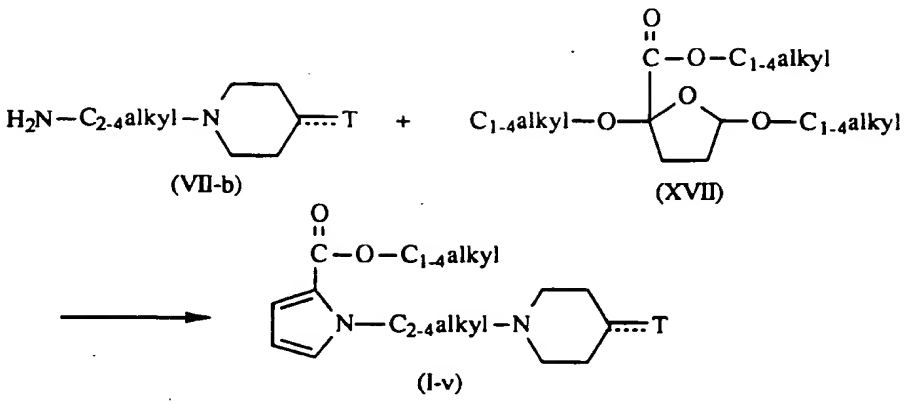
(I-t) (I-s)

u) reacting a compound of formula (VII-b) with a reagent of formula (XVI) in the presence of an acid;



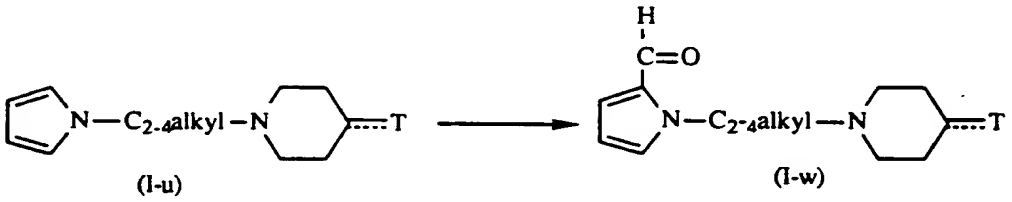
(VII-b) (XVI) (I-u)

v) reacting a compound of formula (VII-b) with a reagent of formula (XVII) in the presence of an acid yielding a compound of formula (I-v)

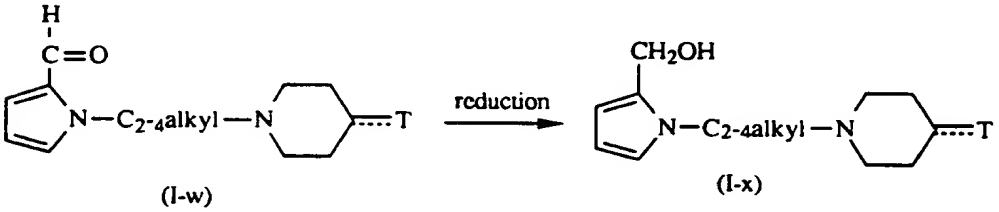


which optionally can be hydrolyzed in the corresponding 2-hydroxycarbonyl-1-pyridyl compound in the presence of an acid or a base;

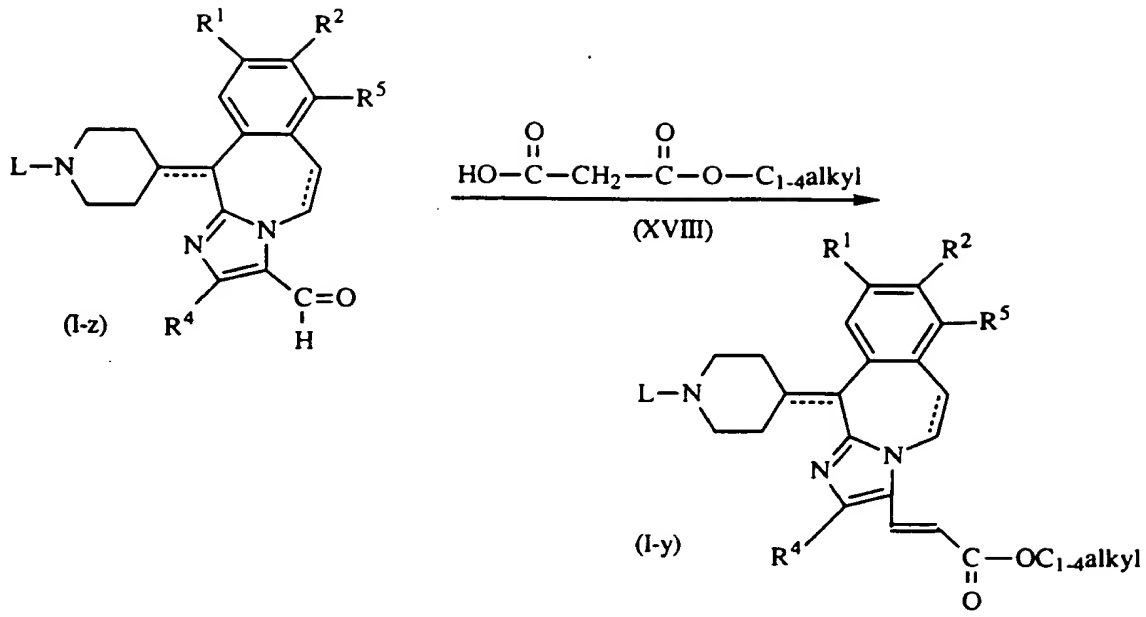
w) formylating a compound of formula (I-u) in a reaction-inert solvent yielding a compound of formula (I-w)



which optionally may be reduced in a reaction-inert solvent in the presence of a reductant yielding an alcohol of formula (I-x)

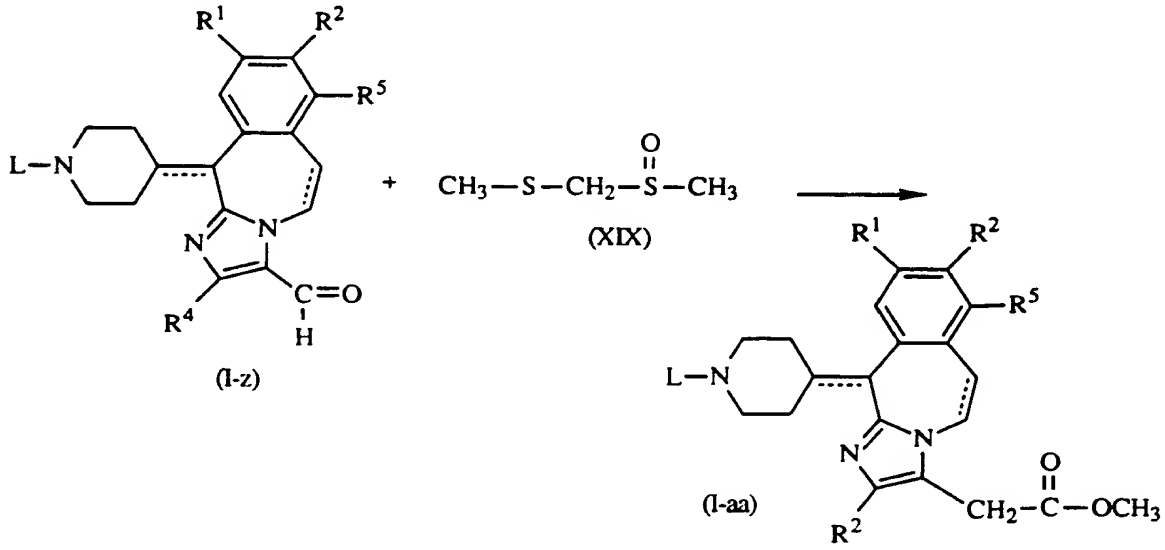


x) reacting a compound of formula (I-z) with a reagent of formula (XVIII) in the presence of a base yielding a compound of formula (I-y)



which optionally may be hydrolyzed in the presence of an acid or a base yielding the corresponding hydroxycarbonyl compound;

y) reacting a compound of formula (I-z) with a reagent of formula (XIX) in the presence of benzyl trimethyl ammonium hydroxide in a reaction-inert solvent yielding a compound of formula (I-aa)



which optionally can be hydrolyzed in the presence of an acid or a base into the corresponding hydroxycarbonyl compound;

and, if desired, convering the compounds of formula (I) into each other following art-known functional group transformation reactions, and further, if desired,

converting the compounds of formula (I) into a therapeutically active non-toxic addition salt form by treatment with an acid or a base; or conversely, converting the salt into the free base or acid with alkali, respectively acid; and/or preparing stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01330

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; C07D519/00; A61K31/55; //(C07D487/00 235:00,223:00)(C07D519/00,513:00,487:00)(C07D519:00,

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 000 716 (MERCK) 21 February 1979 see claims 1,13 ---	1,6
A	EP,A,0 378 254 (JANSSEN) 18 July 1990 see claim 1; example 15 ---	1,6

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 SEPTEMBER 1992	25. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9201330
SA 60320

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 08/09/92

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0000716	21-02-79	US-A-	4148903	10-04-79
		JP-A-	54027597	01-03-79
EP-A-0378254	18-07-90	AU-B-	622509	09-04-92
		AU-A-	4778090	12-07-90
		JP-A-	2233678	17-09-90
		US-A-	5008268	16-04-91

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

05 JAN 1993

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
JAB 812-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 92/01330	09/06/92	13/06/91
Applicant		
JANSSEN PHARMACEUTICA N.V.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ **Certain claims were found unsearchable** (see Box I).

2. ☐ **Unity of invention is lacking** (see Box II).

3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - ☐ filed with the international application.
   - ☐ furnished by the applicant separately from the international application,
     - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - ☐ Transcribed by this Authority

4. With regard to the **title,**
   - ☒ the text is approved as submitted by the applicant.
   - ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - ☒ the text is approved as submitted by the applicant.
   - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - ☐ as suggested by the applicant.
   - ☐ because the applicant failed to suggest a figure.
   - ☐ because this figure better characterizes the invention.
   - ☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01330

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; C07D519/00; A61K31/55; //(C07D487/00 235:00,223:00)(C07D519/00,513:00,487:00)(C07D519:00,

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
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A	EP,A,0 378 254 (JANSSEN) 18 July 1990 see claim 1; example 15 ---	1,6

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 SEPTEMBER 1992	25. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

1

See notes on accompanying sheet

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9201330 SA 60320

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/09/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0000716	21-02-79	US-A- 4148903	10-04-79
		JP-A- 54027597	01-03-79
EP-A-0378254	18-07-90	AU-B- 622509	09-04-92
		AU-A- 4778090	12-07-90
		JP-A- 2233678	17-09-90
		US-A- 5008268	16-04-91

PATENT COOPERATION TREAT

216

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
JANSSEN PHARMACEUTICA N.V.
Attn. Wante, Dirk
Turnhoutseweg 30
2340 BEERSE
BELGIUM

RECEIVED
INTL. LAW DIVISION
OCT 6 1992
TO FILE REFER TO

Search Rept. Response - F due 11/25/92.

Applicant's or agent's file reference JAB 812-PCT	Date of mailing (day/month/year) 25.09.92
International application No. PCT/EP 92/01330	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant JANSSEN PHARMACEUTICA N.V.	International filing date (day/month/year) 09/06/92

30 SEP. 1992

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet. Nov. 25, 92

Where? To the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2; the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Natalie Weinberg

Form PCT/ISA/220 (July 1992)

cc J&J (except Janssen case)

P TENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
JAB 812-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 92/01330	09/06/92	13/06/91
Applicant		
JANSSEN PHARMACEUTICA N.V.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ **Certain claims were found unsearchable** (see Box I).

2. ☐ **Unity of invention is lacking** (see Box II).

3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - ☐ filed with the international application.
   - ☐ furnished by the applicant separately from the international application,
     - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - ☐ Transcribed by this Authority

4. With regard to the **title,**
   - ☒ the text is approved as submitted by the applicant.
   - ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - ☒ the text is approved as submitted by the applicant.
   - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - ☐ as suggested by the applicant.
   - ☐ because the applicant failed to suggest a figure.
   - ☐ because this figure better characterizes the invention.
   - ☐ None of the figures.

INT NATIONAL SEARCH REPORT

International Application No PCT/EP 92/01330

I. CLASSIFICATION OF SUBJECT MAT[redacted] (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; C07D519/00; A61K31/55; //(C07D487/00 235:00,223:00)(C07D519/00,513:00,487:00)(C07D519:00,

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 000 716 (MERCK) 21 February 1979 see claims 1,13 ---	1,6
A	EP,A,0 378 254 (JANSSEN) 18 July 1990 see claim 1; example 15 ---	1,6

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 SEPTEMBER 1992	25. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

See notes on accompanying sheet

NOTES TO FORM PCT/ISA/220

These notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments wil be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; Claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 TO 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings which cannot be amended under Article 19(1).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confouded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English of French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9201330
SA 60320

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 08/09/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0000716	21-02-79	US-A- 4148903	10-04-79
		JP-A- 54027597	01-03-79
EP-A-0378254	18-07-90	AU-B- 622509	09-04-92
		AU-A- 4778090	12-07-90
		JP-A- 2233678	17-09-90
		US-A- 5008268	16-04-91

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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CHAPTER II

PATENT COOPERATION TREATY

QEV 2

Registered letter

Wante, Dirk
JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
2340 BEERSE
BELGIQUE

Received
INTL. LAW DIVISION

FROM THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

WRITTEN OPINION
issued pursuant to PCT rules 66.2.(1) or 66.4(a) (2)

19 APR. 1993

DATE OF MAILING by the International Preliminary Examining Authority: 15.04.93

Inscribe NAME and ADDRESS of the AGENT or if there is no agent, of the APPLICANT

TO FILE ___ REFER TO ___
JANSSEN ANSWERED ___
BRING FILE DOCKET ___

APPLICANT's or AGENT's FILE REFERENCE: JAB 812-PCT

IDENTIFICATION OF THE INTERNATIONAL APPLICATION

International Application No.	International Filing Date
PCT/EP 92/01330	09/06/1992

Applicant (Name): JANSSEN PHARMACEUTICA N.V. et al.

Response Due 7/15/93

Receiving Office	Priority date claimed
RO/EP	13/06/1991

WRITTEN OPINION

With reference to the above-identified international application, this constitutes the first (first, etc.) written opinion by this International Preliminary Examining Authority.

I. BASIS OF OPINION

The examination is being carried out on the following application documents:

- [X] the application documents as filed
- [ ] description, pages ..... , as originally filed
- [ ] description, pages ..... , filed with your letter of .....
- [ ] claim(s) ..... , as originally filed
- [ ] claim(s) ..... , filed with your letter of .....
- [ ] drawings, sheet/fig. ..... , as originally filed
- [ ] drawings, sheet/fig. ..... , filed with your letter of .....
- [ ] This opinion has been established as if the amendments indicated on the extra sheet have not been made, since, for the reasons, they have been considered to go beyond the disclosure as filed.

II. NON-ESTABLISHMENT OF OPINION ON NOVELTY, INVENTIVE STEP AND INDUSTRIAL APPLICABILITY

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), and to be industrially applicable will not for the reasons indicated below be gone into in respect of:

1. [ ] the above-identified international application.
2. [ ] claims Nos. _____ (specify particular claims).

[ ] Said international application, or said claims Nos. _____ relate to the following subject matter 3) which does not require an international preliminary examination. (specify)

[ ] The description, claims, or drawings ((indicate particular elements) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed.3)

[ ] The claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.3)

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WRITTEN OPINION (continued)

III. NEGATIVE STATEMENT IN REGARD TO NOVELTY, INVENTIVE STEP AND INDUSTRIAL APPLICABILITY OF CLAIMS

The statement under Article 35 (2) should be negative in respect of the claims indicated below.
The criteria not satisfied in respect of such claims are indicated by the letter abbreviation.
N (for Novelty); IS (for Inventive Step); IA (for Industrial Applicablity).

1 - 10 : ET

IV. CITATIONS AND EXPLANATIONS IN REGARD TO NOVELTY, INVENTIVE STEP AND INDUSTRIAL APPLICABILITY OF CLAIMS

No. of Claim / Relevant Supporting Documents Cited / Explanation

please see separate sheet

WRITTEN OPINION (continued)

V. CERTAIN DEFECTS IN TH[redacted]NTERNATIONAL APPLICATION

The following defects in the form or contents of the above-identified international application under the Treaty or the Regulation have been noted.

All the relevant prior has not yet been considered in the application.

VI. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are notified:

please dee point 6 of the separate sheet

VII. INVITATION

APPLICANT IS INVITED TO SUBMIT A WRITTEN REPLY ACCOMPANIED, WHERE APPROPRIATE, BY AMENDMENTS (4) WITHIN ~~two~~ 3 MONTHS/ ---- DAYS OF THE DATE OF MAILING INDICATED ON THE FIRST SHEET.

July 15, 93

THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Name and Mailing Adress

European Patent Office
Erhardtstraße 27
D-8000 München 2
☎ 089 / 2399-0
Tx 523 656 epmu d
FAX 089 / 23 99-44 65

Authorized Officer

L.A. Feller

Registered Letter

1. Cited documents

WO-A-9206981 = D1
J. Med. Chem, 26(1983), 974-980 = D2
EP-A-0339978 = D3
EP-A-0000716 = D4
WO-A-8813138 = D5

The indicated designation is used throughout the examination procedure.

2. Novelty

The subject matter of the Claim 1 and Claim 9 (intermediates) differs from that of the cited prior art D2-D5 essentially due to the imidazo condensation in the tricyclic moiety.
The disclaimer contained in Claims 1 and 9 refers obviously to compounds known from D1 which is an earlier document. In the absence of the priority documents it cannot be decided whether the claimed priority date is acceptable. On the condition that the claimed priority date is justifiable D1 may remain outside considersation during the present examination stage but is relevant during a possible regional phase; it is stressed that exclusion of specific compounds may not be sufficient to delimit from D1 (overlap).
The subject matter of the Claims 1 and 9 can be considered to be novel in view of D2-D5.

3. Inventive step - broadness of the claims

3.1 Subjective problem

According to the application (see page 1, line 26) the problem underlying the application appears to be the follow-

ing:
Provision of further benzazepine derivatives which have favourable antiallergic activity.

3.2 Closest prior art

D2-D5 are especially relevant: The compounds of these documents come structurally very close to those of your application and they also appear to show qualitatively the same antiallergic activity. D2 and D3 referring to specific pyrrolo condensed benzazepines are considered to be the closest prior art.

3.3 Problem which has been objectively solved

In view of the information given in the description page 30/31 it may be considered credible that the technical problem as defined under point 3.1 has been solved by the prepared compounds although no specific test results have been disclosed.

3.4 Evaluation of the solution of the problem

The solution to the problem defined above is considered to be obvious for the following reasons:
For the subject matter of Claim 1 D2 and D3 are closest prior art (see point 3.2).
With these products the problem defined under point 3.1 is also solved.
From D2 and D3 the person skilled in the art searching for a solution to this problem would have considered benzazepine derivatives condensed with further heterocyclic 5-membered rings.
Furthermore, D4 and D5 describe benzazepine derivatives condensed with 6-membered rings indicating that the kind of con-

densation does not alter the qualitative activity profile. The solution of the technical problem according to point 3.1 is therefore an obvious result from the prior art. Consequently the subject matter of Claim 1 can at the moment not considered to be inventive.

3.5 Proposals to meet the objection according to point 8.5

Inspite of the opinion indicated above the presence of an inventive step could be acknowledged if it is made credible by test results that apart from the problem defined under point 3.1 another more exacting problem, which can be deduced from the original application (e.g. surprising improvements), has actually been solved by using originally declosed technical characteristics which should be incorporated in claim 1.
It should be taken into consideration that only the structurally closest compounds of the closest prior art D2 and D3 are useful for a meaningful comparison (see T1/80, O. J. EPO 1981, 206). A possible pair for comparison is e.g. a compound of D2 formula 4 and a compound of D3 (first compound of page 8) on the one hand and a compound of the application whereby the corresponding substituents are the same on the other.

3.6 Broadness of the claims

The breadth should be such that all objections indicated above are met and it also could be expected that the compounds comprised would actually solve the problem underlying the invention.

4. Intermediates

The intermediates of Claim 9 are only to be considered to be inventive if it turns out that the endproducts are inventive.

5. Industrial applicability

As far as the subject matter claimed can actually be prepared and has some utility, no objection arises.

6. Clarity of the claims - conciseness

6.1 In Claim 9 definitions identical with those of Claim 1 should be incorporated by reference to Claim 1 thereby avoiding unnecessary repetition.

6.2 Claim 10 is not acceptable in the present form since it contains a contradiction in itself. Whereas the preamble indicates that compounds of Claims 1-5 are to be prepared, certain of the processes listed in the characterising portion of Claim 10 are only useful to prepare certain types of compounds. Claim 10 should therefore be split into several claims whereby the preamble should define the group of compounds which can be prepared by the processes indicated in the characterising portion of the claim.

NOTES TO FORM PCT/IPEA/408

These Notes are intended to facilitate the use of the present form. For full information, see the text of the Patent Cooperation Treaty and the texts of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and the said texts, the latter are applicable. "Article" refers to Articles of the Treaty, "Rule" refers to Rules of the Regulations and "Section" refers to Sections of the Administrative Instructions.

(1) "If the International Preliminary Examining Authority

(i) considers that the international application has any of the defects described in Article 34(4),

(ii) considers that the international preliminary examination report should be negative in respect of any of the claims because the invention claimed therein does not appear to be novel, does not appear to involve an inventive step (does not appear to be non-obvious, or does not appear to be industrially applicable),

(iii) notices that there is some defect in the form or contents of the international application under the Treaty or these Regulations,

(iv) considers that any amendment goes beyond the disclosure in the international application as filed, or

(v) wishes to accompany the international preliminary examination report by observations on the clarity of the claims, the description, and the drawings, or the question whether the claims are fully supported by the description,

the said Authority shall notify the applicant accordingly in writing. Where the national law of the national Office acting as International Preliminary Examining Authority does not allow multiple dependent claims to be drafted in a manner different from that provided for in the second and third sentences of Rule 6.4(a), the International Preliminary Examining Authority may, in case of failure to use that manner of claiming, apply Article 34(4) (b). In such case, it shall notify the applicant accordingly in writing." (Rule 66.2(a)).

"The notification shall fully state the reasons for the opinion of the International Preliminary Examining Authority." (Rule 66.2 (b)).

"The notification shall invite the applicant to submit a written reply together, where appropriate, with amendments." (Rule 66.2 (c)).

"The notification shall fix a time limit for the reply. The time limit shall be reasonable under the circumstances. It shall normally be 2 months after the date of notification. In no case shall it be shorter than 1 month after the said date. It shall be at least 2 months after the said date where the international search report is transmitted at the same time as the notification. In no case shall it be more than 3 months after the said date." (Rule 66.2 (d)).

(2) "If the International Preliminary Examining Authority wishes to issue one or more additional written opinions, it may do so, and Rules 66.2 and 66.3 shall apply." (Rule 66.4(a)).

(3) "If the International Preliminary Examining Authority considers

(i) that the international application relates to a subject matter on which the International Preliminary Examining Authority is not required, under the Regulations, to carry out an international preliminary examination, and in the particular case decides not to carry out such examination, or

(ii) that the description, the claims, or the drawings, are so unclear, or the claims are so inadequately supported by the description, that no meaningful opinion can be formed on the novelty, inventive step (non-obviousness), or industrial applicability, of the claimed invention, the said Authority shall not go into the questions referred to in Article 33(1) and shall inform the applicant of this opinion and the reasons therefor." (Article 34(4) (a)).

Rule 67 entitled "Subject Matter Under Article 34 (4) (a) (i)" reads as follows:

"No International Preliminary Examining Authority shall be required to carry out an international preliminary examination on an international application of, and to the extent to which, its subject matter is any of the following:

(i) scientific and mathematical theories,

(ii) plant or animal varities or essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes,

(iii) schemes, rules or methods of doing business, performing purely mental acts or playing games,

(iv) methods for treatment of the human or animal body by surgery of therapy, as well as diagnostic methods,

(v) more presentations of information,

(vi) computer programs to the extent that the International Preliminary Examining Authority is not equipped to carry out an international preliminary examination concerning such programs."

(4) "The applicant may respond to the invitation referred to in Rule 66.2 (c) of the International Preliminary Examining Authority by making amendments or - if he disagrees with the opinion of that Authority - by submitting arguments, as the case may be, or do both." (Rule 66.3 (a)).

"Any response shall be submitted directly to the International Preliminary Examining Authority." (Rule 66.3(b)).

"On the request of the applicant, the International Preliminary Examining Authority may give him one or more additional opportunities to submit amendments or arguments." (Rule 66.4 (b)).

"The applicant shall re required to submit a replacement sheet for every sheet of the international application which, on account of an amendment, differs from the sheet originally filed. The letter accompanying the replacement sheets shall draw attention to the differences between the replaced sheets and the replacement sheets. To the extent that any amendment results in the cancellation of an entire sheet, that amendment shall be communicated in a letter." (Rule 66.8 (a)).

"If the international application has been filed in a language other than the language in which it is published, any amendment, as well as any letter referred to in Rule 66.8 (a), shall be submitted in the language of publication." (Rule 66.9).

"Amendments to the claims under Article 19 or Article 34(2) (b) may be made either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed. All the claims appearing on a replacement sheet shall be numbered in arabic numerals. Where a claim is cancelled, no renumbering of the other claims shall be required. In all cases where claims are renumbered, they shall be renumbered consecutively." (Section 205(a)).

Europäisches Patentamt | European Patent Office | Office européen des brevets

CORRESPONDENCE WITH THE EPO ON PCT CHAPTER II DEMANDS

In order to ensure that your PCT chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter heading or form etc. which you are filing.

21b

PATENT COOPERATION TREA.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
Wante, Dirk
JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
2340 BEERSE
BELGIQUE

27 AUG. 1993

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	25.08.93

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
JAB 812-PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 92/01330	09/06/1992	13/06/1991

Applicant

JANSSEN PHARMACEUTICA N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office, Erhardtstrasse 27 W-8000 Munich 2 Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	D. Gran

TENT COOPERATION TREA

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JAB 812-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 92/ 01330	09/06/1992	13/06/1991
International Patent Classification (IPC) or national classification and IPC		
C07D487/04		
Applicant		
JANSSEN PHARMACEUTICA N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings amended during international preliminary examination and/or containing rectifications made before this Authority.

   These annexes consists of a total of _____ sheets.

3. This report contains indications and corresponding pages relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☒ Certain documents cited

   VII ☒ Certain defects in the international application

   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/12/1992	05.08.93
Name and mailing address of the IPEA/	Authorized officer
European Patent Office, Erhardtstrasse 27 W-8000 Munich 2 Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	L.A. Feller

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

I. Basis of the report

1. This report has been drawn up on the basis of:

[x] the international application as originally filed.

[ ] the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[ ] the claims, No. _____, as originally filed,
No. _____, as amended under Article 19,
No. _____, filed with the demand,
No. _____, filed with the letter of _____,
No. _____, filed with the letter of _____,

[ ] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of: pages: _____
sheets of drawings/figures No.: _____.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed:

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-10	YES
	Claims	NO
Inventive Step (IS)	Claims	YES
	Claims 1-10	NO
Industrial Applicability (IA)	Claims 1-10	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

1. Cited documents

WO-A-9206981 = D1
J. Med. Chem, 26(1983), 974-980 = D2
EP-A-0339978 = D3
EP-A-0000716 = D4
WO-A-8813138 = D5

The indicated designation is used throughout the examination procedure.

2. Novelty

The subject matter of the Claim 1 and Claim 9 (intermediates) differs from that of the cited prior art D2-D5 essentially due to the imidazo condensation in the tricyclic moiety. The disclaimer contained in Claims 1 and 9 refers obviously to compounds known from D1 which is an earlier document. In the absence of the priority documents it cannot be decided

whether the claimed priority date is acceptable. On the condition that the claimed priority date is justifiable D1 may remain outside considersation during the present examination stage but is relevant during a possible regional phase; it is stressed that exclusion of specific compounds may not be sufficient to delimit from D1 (overlap).
The subject matter of the Claims 1 and 9 can be considered to be novel in view of D2-D5.

3. Inventive step - broadness of the claims

3.1 Subjective problem

According to the application (see page 1, line 26) the problem underlying the application appears to be the following: Provision of further benzazepine derivatives which have favourable antiallergic activity.

3.2 Closest prior art

D2-D5 are especially relevant: The compounds of these documents come structurally very close to those of your application and they also appear to show qualitatively the same antiallergic activity. D2 and D3 referring to specific pyrrolo condensed benzazepines are considered to be the closest prior art.

3.3 Problem which has been objectively solved

In view of the information given in the description page 30/31 it may be considered credible that the technical problem as defined under point 3.1 has been solved by the prepared compounds although no specific test results have been disclosed.

3.4 Evaluation of the solution of the problem

The solution to the problem defined above is considered to be obvious for the following reasons:
For the subject matter of Claim 1 D2 and D3 are closest prior art (see point 3.2).
With these products the problem defined under point 3.1 is also solved.
From D2 and D3 the person skilled in the art searching for a solution to this problem would have considered benzazepine derivatives condensed with further heterocyclic 5-membered rings.
Furthermore, D4 and D5 describe benzazepine derivatives condensed with 6-membered rings indicating that the kind of condensation does not alter the qualitative activity profile.
The solution of the technical problem according to point 3.1 is therefore an obvious result from the prior art. Consequently the subject matter of Claim 1 can at the moment not considered to be inventive.

3.5 Proposals to meet the objection according to point 8.5

Inspite of the opinion indicated above the presence of an inventive step could be acknowledged if it is made credible by test results that apart from the problem defined under point 3.1 another more exacting problem, which can be deduced from the original application (e.g. surprising improvements), has actually been solved by using originally declosed technical characteristics which should be incorporated in claim 1.
It should be taken into consideration that only the structurally closest compounds of the closest prior art D2 and D3 are useful for a meaningful comparison. A possible pair for comparison is e.g. a compound of D2 formula 4 and a compound of D3 (first compound of page 8) on the one hand and a compound of the application whereby the corresponding substituents are the same on the other.

3.6 Broadness of the claims

The breadth should be such that all objections indicated above are met and it also could be expected that the compounds comprised would actually solve the problem underlying the invention.

4. Intermediates

The intermediates of Claim 9 are only to be considered to be inventive if it turns out that the endproducts are inventive.

5. Industrial applicability

As far as the subject matter claimed can actually be prepared and has some utility, no objection arises.

VI. Certain documents cited

1. Certain published documents

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO92/06981	30/04/1992	04/10/1991	10/10/1990

2. Non-written disclosures

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

All the relevant prior art has not been considered in the application

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

a) In Claim 9 definitions identical with those of Claim 1 should be incorporated by reference to Claim 1 thereby avoiding unnecessary repetition.

b) Claim 10 is not acceptable in the present form since it contains a contradiction in itself. Whereas the preamble indicates that compounds of Claims 1-5 are to be prepared, certain of the processes listed in the characterising portion of Claim 10 are only useful to prepare certain types of compounds. Claim 10 should therefore be split into several claims whereby the preamble should define the group of compounds which can be prepared by the processes indicated in the characterising portion of the claim.

PATENT COOPERATION TREATY

INTERNATIONAL APPLICATION NO. PCT/EP92/01330

NOTIFICATION TO THE DESIGNATED OFFICE OF RECEIPT OF RECORD COPY
issued under PCT Rule 24.2(a)

To:

United States Patent
and Trademark Office
Washington, D.C.

APPLICANT'S OR AGENT'S FILE REFERENCE:
JAB812-PCT

in its capacity as a designated Office

DATE OF MAILING OF THIS NOTIFICATION:
29 June 1992 (29.06.92)

From:
The International Bureau of WIPO
1211 Geneva 20
Switzerland

NAME(S) OF APPLICANT(S):

JANSSENS, Frans, Eduard et al.

INTERNATIONAL FILING DATE:
09 June 1992 (09.06.92)

PRIORITY DATE(S) CLAIMED:
13 June 1991 (13.06.91)
18 March 1992 (18.03.92)

DATE OF RECEIPT OF RECORD COPY BY INTERNATIONAL BUREAU:
29 June 1992 (29.06.92)

J. Leitao
(Authorized Officer)

Form PCT/IB/302 (January 1984)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
Washington, D.C.

in its capacity as elected Office

Date of mailing: 09 February 1993 (09.02.93)	
International application No.: PCT/EP92/01330	Applicant's or agent's file reference: JAB812-PCT
International filing date: 09 June 1992 (09.06.92)	Priority date: 13 June 1991 (13.06.91)
Applicant: JANSSENS, Frans, Eduard et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

08 December 1992 (08.12.92)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer: J. Leitao
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
DOCUMENT TRANSMITTED

To:

United States Patent and Trademark
Office
Washington, D.C.

in its capacity as elected Office

Date of mailing:
31 August 1993 (31.08.93)

International application No.:
PCT/EP92/01330

International filing date:
09 June 1992 (09.06.92)

Applicant:
JANSSEN PHARMACEUTICA N.V. et al

The International Bureau transmits herewith the following documents and number thereof:

_____ copy of the international preliminary examination report (Article 36(3)(a))

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer:

C. Carrié

Telephone No.: (41-22) 730.91.11

20

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JAB 812-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 92/ 01330	09/06/1992	13/06/1991
International Patent Classification (IPC) or national classification and IPC		
C07D487/04		
Applicant		
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   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

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   VII ☒ Certain defects in the international application

   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/12/1992	25.08.93
Name and mailing address of the IPEA/	Authorized officer
European Patent Office, Erhardtstrasse 27 W-8000 Munich 2 Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	J.A. Zeiler L.A. Feller

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.
PCT/EP92/01330

I. Basis of the report

1. This report has been drawn up on the basis of:

[x] the international application as originally filed.

[ ] the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

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No. _____, as amended under Article 19,
No. _____, filed with the demand,
No. _____, filed with the letter of _____,
No. _____, filed with the letter of _____,

[ ] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

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sheets of drawings/figures No.: _____.

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	Claims	NO
Inventive Step (IS)	Claims	YES
	Claims 1-10	NO
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Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO92/06981	30/04/1992	04/10/1991	10/10/1990

2. Non-written disclosures

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

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RECORD COPY

11 Rec'd PCT/PTO 05 JAN 19

INTERNATIONAL APPLICATION UNDER THE PATENT COOPERATION TREATY

REQUEST

THE UNDERSIGNED REQUESTS THAT THE PRESENT INTERNATIONAL APPLICATION BE PROCESSED ACCORDING TO THE PATENT COOPERATION TREATY

(The following is to be filled in by the receiving Office)

INTERNATIONAL APPLICATION No. PCT/EP 92 / 01330

INTERNATIONAL FILING DATE: 09 JUN 1992 (09. 06. 92)

EUROPEAN PATENT OFFICE

(Stamp) PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (indicated by applicant if desired) JAB 812-PCT

Box No. I TITLE OF INVENTION

Imidazo[2,1-b][3]benzazepine derivatives, compositions and method of use

Box No. II APPLICANT (WHETHER OR NOT ALSO INVENTOR); DESIGNATED STATES FOR WHICH HE/SHE/IT IS APPLICANT. Use this box for indicating the applicant or, if there are several applicants, one of them. If more than one person (includes, where applicable, a legal entity) is involved, continue in Box No. III.

The person identified in this box is (mark one check-box only): ☐ applicant and inventor* ☒ applicant only

Name *and* address:**

JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
B-2340-Beerse
Belgium

Telephone number (including area code):	Telegraphic address:	Teleprinter address:
014/60.21.11	JANSSENPHARMA	32540 janfar b

State of nationality: Belgium State of residence:* BE

The person identified in this box is *applicant* for the purposes of (mark one check-box only):

☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the "Supplemental Box"

Box No. III FURTHER APPLICANTS, IF ANY; (FURTHER) INVENTORS, IF ANY; DESIGNATED STATES FOR WHICH THEY ARE APPLICANTS (IF APPLICABLE). A separate sub-box has to be filled in in respect of each person (includes, where applicable, a legal entity). If the following two sub-boxes are insufficient, continue in the "Supplemental Box," (giving there for each additional person the same indications as those requested in the following two sub-boxes) or by using a "continuation sheet."

The person identified in this sub-box is (mark one check-box only): ☒ applicant and inventor* ☐ applicant only ☐ inventor only*

Name *and* address:**

JANSSENS, Frans Eduard
Tinstraat 79
B-2820-Bonheiden
Belgium

If the person identified in this sub-box is *applicant (or applicant and inventor),* indicate also:

State of nationality: Belgium State of residence:* BE

and whether that person is *applicant* for the purposes of (mark one check-box only):

☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the "Supplemental Box"

The person identified in this sub-box is (mark one check-box only): ☒ applicant and inventor* ☐ applicant only ☐ inventor only*

Name *and* address:**

DIELS, Gaston Stanislas Marcella
Oosteinde 12
B-2380-Ravels
Belgium

If the person identified in this sub-box is *applicant (or applicant and inventor),* indicate also:

State of nationality: Belgium State of residence:* BE

and whether that person is *applicant* for the purposes of (mark one check-box only):

☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the "Supplemental Box"

* If the person indicated as "applicant and inventor" or as "inventor only" is not an *inventor* for the purposes of all the designated States, give the necessary indications in the "Supplemental Box."

** Indicate the name of a natural person by giving his/her family name first followed by the given name(s). Indicate the name of a legal entity by its full official designation. In the address, include both the postal code (if any) and the State (name).

*** If residence is not indicated, it will be assumed that the State of residence is the same as the State indicated in the address.

Sheet number 2 PCT/EP 92/01330

Box No. III CONTINUATION REQUIRED) FURTHER APPLICANTS, IF A (FURTHER) INVENTORS, IF ANY; DESIGNATED STATES WHICH THEY ARE APPLICANTS (IF APP BLE). A separate sub-box has to be filled in in respect of each person (includes, where applicable, a legal entity).

The person identified in this sub-box is (mark one check-box only): [X] applicant and inventor* [ ] applicant only [ ] inventor only*

Name *and* address:**

LEENAERTS, Joseph Elisabeth
Potbergstraat 35
B-2310-Rijkevorsel
Belgium

If the person identified in this sub-box is *applicant (or applicant and inventor),* indicate also:

State of nationality: Belgium State of residence:*** BE

and whether that person is *applicant* for the purposes of (mark one check-box only):

[ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the "Supplemental Box"

The person identified in this sub-box is (mark one check-box only): [ ] applicant and inventor* [ ] applicant only [ ] inventor only*

Name *and* address:**

If the person identified in this sub-box is *applicant (or applicant and inventor),* indicate also:

State of nationality: State of residence:***

and whether that person is *applicant* for the purposes of (mark one check-box only):

[ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the "Supplemental Box"

The person identified in this sub-box is (mark one check-box only): [ ] applicant and inventor* [ ] applicant only [ ] inventor only*

Name *and* address:**

If the person identified in this sub-box is *applicant (or applicant and inventor),* indicate also:

State of nationality: State of residence:***

and whether that person is *applicant* for the purposes of (mark one check-box only):

[ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the "Supplemental Box"

The person identified in this sub-box is (mark one check-box only): [ ] applicant and inventor* [ ] applicant only [ ] inventor only*

Name *and* address:**

If the person identified in this sub-box is *applicant (or applicant and inventor),* indicate also:

State of nationality: State of residence:***

and whether that person is *applicant* for the purposes of (mark one check-box only):

[ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the "Supplemental Box"

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*** If residence is not indicated, it will be assumed that the State of residence is the same as the State indicated in the address.

If this continuation sheet is not used, it need not be included in the Request.

Box No. IV AGENT (IF ANY) OR COMMON REPRESENTATIVE (IF ANY); ADDRESS FOR NOTIFICATIONS (IN CERTAIN CASES). A common representative may be appointed only if there are several applicants and if no agent is or has been appointed; the common representative must be one of the applicants.
The following person (includes, where applicable, a legal entity) is hereby/has been appointed as agent or common representative to act on behalf of the applicant(s) before the competent International Authorities:

Name *and* address, including postal code and country:

If the space below is used instead for an address for notifications, mark here: ☐

WANTE, Dirk
Janssen Pharmaceutica N.V.
Patent Department
Turnhoutseweg 30
B-2340-Beerse
Belgium

Telephone number (including area code): 00 32 14 60 31 29

Telegraphic address: 32540 janfar b

Teleprinter address: 00 32 14 60 55 22

Box No. V DESIGNATION OF GROUPS OF STATES OR STATES(1); CHOICE OF CERTAIN KINDS OF PROTECTION OR TREATMENT. The following designations are hereby made (please mark the applicable check-boxes):

Regional Patent

[X] **EP** **European Patent(2):** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **DE** Germany, **DK** Denmark, **ES** Spain, **FR** France, **GB** United Kingdom, **GR** Greece, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **SE** Sweden,
and any other State which is a Contracting State of the European Patent Convention and of the PCT

[X] **OA** **OAPI Patent:** Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Gabon, Guinea, Mali, Mauritania, Senegal, Togo,
and any other State which is a Contracting State of OAPI and of the PCT; if other OAPI title desired, specify on dotted line(3):

.....

National Patent (if other kind of protection or treatment desired, specify on dotted line(3)

☐	**AT**	Austria(3)	[X]	**KR**	Republic of Korea(3) .....
[X]	**AU**	Australia(3)	[X]	**LK**	Sri Lanka
[X]	**BB**	Barbados	☐	**LU**	Luxembourg(3) .....
[X]	**BG**	Bulgaria(3)	[X]	**MG**	Madagascar
[X]	**BR**	Brazil(3)	☐	**MN**	Mongolia(3) .....
[X]	**CA**	Canada	[X]	**MW**	Malawi(3) .....
☐	**CH and LI**	Switzerland and Liechtenstein	☐	**NL**	Netherlands
[X]	**CS**	Czechoslovakia	[X]	**NO**	Norway
☐	**DE**	Germany(3)	[X]	**PL**	Poland(3) .....
☐	**DK**	Denmark	[X]	**RO**	Romania
☐	**ES**	Spain(3)	[X]	**SD**	Sudan
[X]	**FI**	Finland	☐	**SE**	Sweden
☐	**GB**	United Kingdom	☐	~~**SU**~~	~~Soviet Union~~
[X]	**HU**	Hungary	[X]	**US**	United States of America(3) .....
[X]	**JP**	Japan(3)			continuation-in-part .....
[X]	**KP**	Democratic People's Republic of Korea(3) ...			
		.....			

X RU Russian Federation

Space reserved for designating States (for the purposes of a national patent) which have become party to the PCT after the issuance of this sheet:

.....

(1) The applicant's choice of the order of designations may be indicated by marking the check-boxes with sequential arabic numerals (see also the "Notes to Box No. V").
(2) The selection of particular States for a European patent can be made upon entering the national (regional) phase before the European Patent Office (see also the "Notes to Box No. V").
(3) If another kind of protection or a title of addition or, in the United States of America, treatment as a continuation or a continuation-in-part is desired, specify according to the instructions given in the "Notes to Box No. V."

See notes on accompanying sheet

Supplemental Box. Use this box in the following cases:

(i) *if more than three persons are involved as applicants and/or inventors;* in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III;

(ii) *if, in Box No. II or any of the sub-boxes of Box No. III, the indication "the States indicated in the 'Supplemental Box,'" is checked;* in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State or States (or EP or OA, if applicable) for the purposes of which he/she/it is applicant;

(iii) *if, in Box No. II or any of the sub-boxes of Box No. III, a person indicated as "applicant and inventor" or "inventor only" is not inventor for the purposes of all designated States or for the purposes of the United States of America;* in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor and, next to such name, the State or States (or EP or OA, if applicable) for the purposes of which the named person is inventor;

(iv) *if there is more than one agent and their addresses are not the same;* in such case, write "Continuation of Box No. IV" and indicate for each additional agent the same type of information as required in Box No. IV;

(v) *if, in Box No. V, the name of any country (or OAPI) is accompanied by the indication "patent of addition," "certificate of addition," or "inventor's certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part";* in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of parent title or filing of parent application;

(vi) *if there are more than three earlier applications whose priority is claimed;* in such case, indicate "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;

(vii) *if, in any of the Boxes, the space is insufficient to furnish all the information;* in such case, write "Continuation of Box No...." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;

(viii) *if the applicant intends to claim, in respect of any designated Office, the benefit of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty;* in such case, write "Statement Concerning Non-prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.

Continuation of Box V

United States of America, Continuation-in-part of
Application No. 853,631
filed 18 March, 1992 (18.03.92)

which in turn is a continuation of
Application No. 714,486
filed 13 June 1991 (13.06.91)

If this Supplemental Box is not used, this sheet need not be included in the Request.

PCT/EP 92/01330

Box No. VI PRIORITY CLAIM (IF ANY). The priority of the following earlier application is hereby claimed:

Country (country in which it was filed if national application; one of the countries for which it was filed if regional or international application)	Filing Date (day, month, year)	Application No.	Office of filing (fill in only if the earlier application is an international application or a regional application)
(1) U.S.	13 June 1991 (13.06.91)	714,486	
(2) U.S.	18 March 1992 (18.03.92)	853,631	
(3)			

(Letter codes may be used to indicate country and/or Office of filing)

When the earlier application was filed with the Office which, for the purposes of the present international application, is the receiving Office, the applicant may, *against payment of the required fee,* ask the following:

☐ the receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the above-mentioned earlier application/of the earlier applications identified above by the numbers (insert the applicable numbers) .....

Box No. VII EARLIER SEARCH (IF ANY). Fill in where a search (international, international-type or other) by the International Searching Authority has already been requested (or completed) and the said Authority is now requested to base the international search, to the extent possible, on the results of the said earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.

International application number or number and country (or regional Office) of other application:

International/regional/national filing date:

Date of request for search:

Number (if available) given to search request:

Box No. VIII SIGNATURE OF APPLICANT(S) OR AGENT

For Janssen Pharmaceutica N.V.

Dirk WANTE, Proxy Holder

Frans E. JANSSENS

Gaston S.M. DIELS

Joseph E. LEENAERTS

If the present Request form is signed on behalf of any applicant by an agent, a separate power of attorney appointing the agent and signed by the applicant is required. If in such case it is desired to make use of a general power of attorney (deposited with the receiving Office), a copy thereof must be attached to this form.

Box No. IX CHECK LIST (To be filled in by the Applicant)

This international application contains the following number of sheets:

1.	request	5	sheets
2.	description	71	sheets
3.	claims	14	sheets
4.	abstract	1	sheets
5.	drawings		sheets
	Total	91	sheets

Figure number ..... of the drawings (if any) is suggested to accompany the abstract for publication.

This international application as filed is accompanied by the items marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☒ priority document(s) (see Box No. VI)
4. ☐ receipt of the fees paid or revenue stamps
5. ☐ cheque for the payment of fees
6. ☒ request to charge deposit account
7. ☐ other document (specify)

(The following is to be filled in by the receiving Office)

1. Date of actual receipt of the purported international application: 09 JUN 1992 (09.06.92)
2. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
3. Date of timely receipt of the required corrections under Article 11 of the PCT:
4. Drawings ☐ Received ☒ No Drawings

(The following is to be filled in by the International Bureau)

Date of receipt of the record copy: 29 JUNE 1992 (29.06.92)